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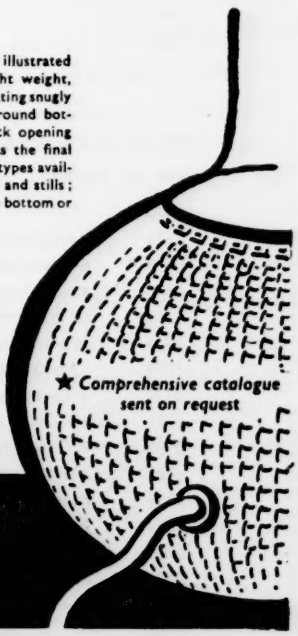

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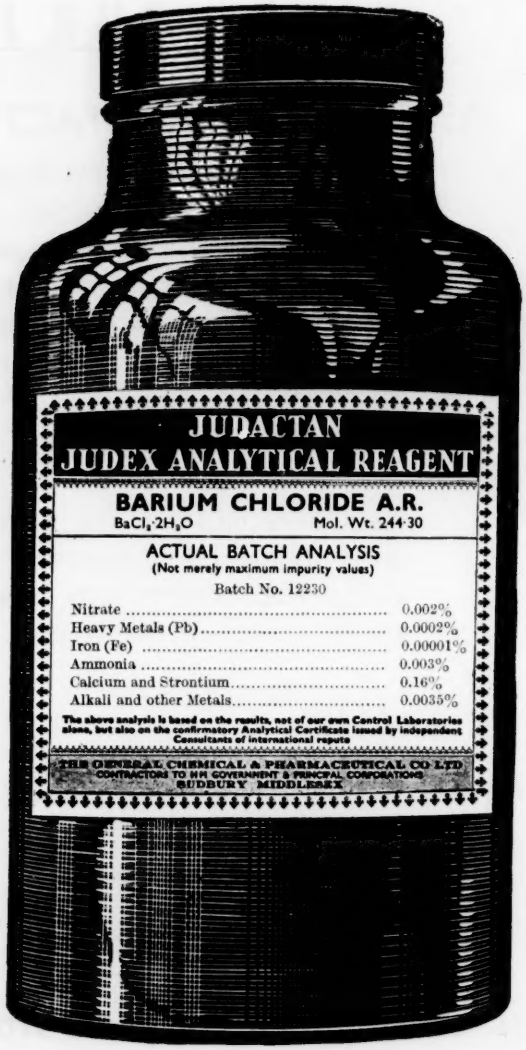
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INTERNATIONAL ATOMIC WEIGHTS, 1951.

[Reprinted from the Report of the Commission on Atomic Weights to the 16th Conference of the International Union of Pure and Applied Chemistry.]

	Symbol.	Atomic number.	Atomic weight.*		Symbol.	Atomic number.	Atomic weight.*
Actinium	Ac	89	227	Molybdenum	Mo	42	95·95
Aluminium	Al	13	26·98	Neodymium	Nd	60	144·27
Americium	Am	95	[243]	Neptunium	Np	93	[237]
Antimony	Sb	51	121·76	Neon	Ne	10	20·183
Argon	A	18	39·944	Nickel	Ni	28	58·69
Arsenic	As	33	74·91	Niobium	Nb	41	92·91
Astatine	At	85	[210]	Nitrogen	N	7	14·008
Barium	Ba	56	137·36	Osmium	Os	76	190·2
Berkelium	Bk	97	[245]	Oxygen	O	8	16·0000
Beryllium	Be	4	9·013	Palladium	Pd	46	106·7
Bismuth	Bi	83	209·00	Phosphorus	P	15	30·975
Boron	B	5	10·82	Platinum	Pt	78	195·23
Bromine	Br	35	79·916	Plutonium	Pu	94	[242]
Cadmium	Cd	48	112·41	Polonium	Po	84	210
Cæsium	Cs	55	132·91	Potassium	K	19	39·100
Calcium	Ca	20	40·08	Praseodymium	Pr	59	140·92
Californium	Cf	98	[246]	Promethium	Pm	61	[145]
Carbon	C	6	12·010	Protactinium	Pa	91	231
Cerium	Ce	58	140·13	Radium	Ra	88	226·05
Chlorine	Cl	17	35·457	Radon	Rn	86	222
Chromium	Cr	24	52·01	Rhenium	Re	75	186·31
Cobalt	Co	27	58·94	Rhodium	Rh	45	102·91
Copper	Cu	29	63·54	Rubidium	Rb	37	85·48
Curium	Cm	96	[243]	Ruthenium	Ru	44	101·7
Dysprosium	Dy	66	162·46	Samarium	Sm	62	150·43
Erbium	Er	68	167·2	Scandium	Sc	21	44·96
Europium	Eu	63	152·0	Selenium	Se	34	78·96
Fluorine	F	9	19·00	Silicon	Si	14	28·09
Francium	Fr	87	[223]	Silver	Ag	47	107·880
Gadolinium	Gd	64	156·9	Sodium	Na	11	22·997
Gallium	Ga	31	69·72	Strontium	Sr	38	87·63
Germanium	Ge	32	72·60	Sulphur	S	16	32·066†
Gold	Au	79	197·2	Tantalum	Ta	73	180·88
Hafnium	Hf	72	178·6	Technetium	Tc	43	[99]
Helium	He	2	4·003	Tellurium	Te	52	127·61
Holmium	Ho	67	164·94	Terbium	Tb	65	159·2
Hydrogen	H	1	1·0080	Thallium	Tl	81	204·39
Indium	In	49	114·76	Thorium	Th	90	232·12
Iodine	I	53	126·91	Thulium	Tm	69	169·4
Iridium	Ir	77	193·1	Tin	Sn	50	118·70
Iron	Fe	26	55·85	Titanium	Ti	22	47·90
Krypton	Kr	36	83·80	Tungsten	W	74	183·92
Lanthanum	La	57	138·92	Uranium	U	92	238·07
Lead	Pb	82	207·21	Vanadium	V	23	50·95
Lithium	Li	3	6·940	Xenon	Xe	54	131·3
Lutetium	Lu	71	174·99	Ytterbium	Yb	70	173·04
Magnesium	Mg	12	24·32	Yttrium	Y	39	88·92
Manganese	Mn	25	54·93	Zinc	Zn	30	65·38
Mercury	Hg	80	200·61	Zirconium	Zr	40	91·22

* A value given in brackets denotes the mass number of the isotope of longest known half-life.

† Because of natural variations in the relative abundance of its isotopes, the atomic weight of sulphur has a range of ±0·003.

[The names given above are those adopted by the Chemical Society.]

JOURNAL
OF
THE CHEMICAL SOCIETY

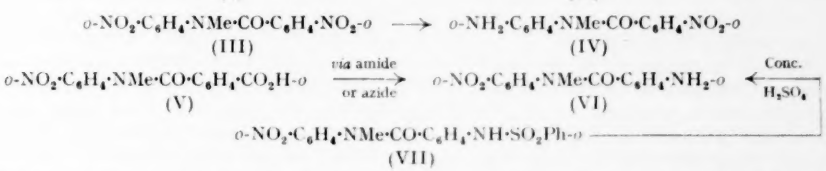
1. *Internuclear Cyclisation. Part VII.* The Synthesis of Some Nitro-N-methylphenanthridones.*

By R. A. Heacock and D. H. Hey.

Methods for the preparation of *o*-amino-*N*-methylnitrobenzanilides have been investigated. Unambiguous methods have been used for the synthesis of *o*-amino-*N*-methyl-*o'*-nitro-, -*p'*-nitro-, and -3' : 5'-dinitro-benzanilide, and the decomposition of the diazonium fluoroborates prepared from these bases gave *N*-methyl-1-nitro-, *N*-methyl-3-nitro-, and *N*-methyl-2 : 4-dinitro-phenanthridone respectively.

In Part III (*J.*, 1952, 1508) methods were described for the conversion of *o*-amino-*N*-methylbenzanilide into *N*-methylphenanthridone, and in Part VI * these methods were successfully applied to the synthesis of some methyl-, halogeno-, and carbomethoxy-*N*-methylphenanthridones. In order further to ascertain the scope and limitations of these reactions and to obtain information on the mechanism of the internuclear cyclisation process the conversion by similar methods of three *o*-amino-*N*-methylnitrobenzanilides into *N*-methylnitrophenanthridones has been investigated. These reactions are of special interest because they involve the formation of a new internuclear bond in two instances at a position *meta* with respect to a nitro-group and in one instance at a position which is both *ortho* and *para* with respect to a nitro-group.

Three methods were investigated for the preparation of the required *o*-amino-*N*-methylnitrobenzanilides. In the first a series of five dinitrobenzanilides was prepared by the interaction of a nitrobenzoyl chloride with a nitroaniline, at least one of the two components being an *ortho*-isomeride, and the products were methylated with methyl sulphate in aqueous acetone. Two of these *N*-methyldinitrobenzanilides were subjected to partial reduction with sodium disulphide in an attempt to obtain the required amino-*N*-methylnitrobenzanilide. With *N*-methyl-*o'p*-dinitrobenzanilide (I) the product proved to be, not *o'*-amino-*N*-methyl-*p*-nitrobenzanilide, but *p*-amino-*N*-methyl-*o'*-nitrobenzanilide (II), the identity of which was established by deamination to *N*-methyl-*o'*-nitrobenzanilide. A similar method of reduction applied to *N*-methyl-*oo'*-dinitrobenzanilide (III) gave *o'*-amino-*N*-methyl-*o*-nitrobenzanilide (IV), the constitution of which was established by its non-identity with an authentic specimen of the isomeric *o*-amino-*N*-methyl-*o'*-nitrobenzanilide (VI), prepared as described below.

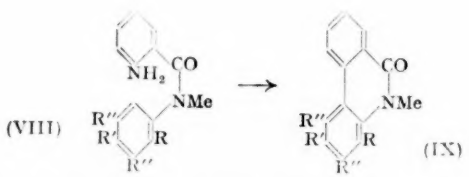


The second method of preparation is illustrated by the conversion of the known *o'*-nitrophthalanilic acid into *N*-methyl-*o'*-nitrophthalanilic acid (V), and thence into either the

* Part VI, *J.*, 1952, 4059.

amide or the azide. By means of the Hofmann and the Curtius degradation respectively the latter were converted into *o*-amino-*N*-methyl-*o'*-nitrobenzanilide (VI). The third method involves condensation of benzenesulphonylanthraniloyl chloride with a nitromethylaniline followed by removal of the benzenesulphonyl group from the *o*-benzenesulphonamido-*N*-methyl-*o'*-nitrobenzanilide (*e.g.*, VII) on long storage at room temperature in the presence of concentrated sulphuric acid by the procedure due to Schroeter and Eisleb (*Annalen*, 1909, **367**, 101). In this manner *o*-amino-*N*-methyl-*o'*-nitro- (VI), -*p'*-nitro- and -3' : 5'-dinitro-benzanilide were obtained. No constitutional ambiguity is involved in the second and the third method.

Diazonium fluoroborates were prepared from *o*-amino-*N*-methyl-*o'*-nitro- (VIII; $R = NO_2$, $R' = R'' = H$), -*p'*-nitro- (VIII; $R' = NO_2$, $R = R'' = H$), and -3' : 5'-dinitro-benzanilide (VIII; $R'' = NO_2$, $R = R' = H$), and were decomposed in suspension in dry acetone by the addition of copper powder. In this manner 10-methyl-1-nitro- (IX; $R = NO_2$, $R' = R'' = H$), 10-methyl-3-nitro- (IX; $R' = NO_2$, $R = R'' = H$), and 10-methyl-2 : 4-dinitro-phenanthridone (IX; $R'' = NO_2$, $R = R' = H$) were obtained in yields of 21·5%, 28·5%, and 34·5% respectively. No hydroxy-*N*-methylnitrobenzanilides were isolated in these reactions. 10-Methyl-1-nitrophenanthridone (IX; $R = NO_2$, $R' = R'' = H$) was also obtained in 12% yield by the thermal decomposition in aqueous solution of the diazonium sulphate prepared from *o*-amino-*N*-methyl-*o'*-nitrobenzanilide (VIII; $R = NO_2$, $R' = R'' = H$), which reaction also gave *o*-hydroxy-*N*-methyl-*o'*-nitrobenzanilide in 9% yield. The decomposition of the diazonium fluoroborate prepared from *p*-amino-*N*-methyl-*o'*-nitrobenzanilide, which cannot give a phenanthridone, gave *N*-methyl-*o'*-nitrobenzanilide by deamination and *p*-hydroxy-*N*-methyl-*o'*-nitrobenzanilide, the latter being formed presumably as a result of the adventitious presence of moisture.



The yields of *N*-methylphenanthridones obtained in the decomposition of the diazonium fluoroborates prepared from *o*-amino-*N*-methylbenzanilides with substituent atoms or groups in the methylaniline nucleus show little relation to the electronic character of the substituent.

Experimental

N-Methyldinitrobenzanilides.—The nitroaniline (1 mol.) and nitrobenzoyl chloride (prepared from ~1 mol. of acid) in pyridine were boiled for 5 minutes, cooled, and poured into water. The dinitrobenzanilide crystallised from aqueous alcohol with charcoal. *o*-Nitrobenzoyl chloride (Böetius and Römisch, *Ber.*, 1935, **68**, 1924) was used in solution in dry ether which was filtered before use. An excess of methyl sulphate (~3 mols.) was added slowly to a boiling and vigorously stirred mixture of the dinitrobenzanilide (1 mol.) in a mixture of equal volumes of acetone and 20% aqueous sodium hydroxide. The colour of the acetone layer changed from deep orange to pale yellow, after which the mixture was cooled and added to an excess of 20% aqueous sodium hydroxide and ice. The yellow oil which separated, solidified and was recrystallised from aqueous alcohol with charcoal. The results obtained are tabulated on p. 5.

Partial Reduction of N-*Methyl*-o'p- *and of* N-*Methyl*-oo'-*dinitrobenzanilide.*—A solution of sodium disulphide, prepared by boiling sodium sulphide ($Na_2S,9H_2O$, 8 g.) in water (100 c.c.) with sulphur (2 g.) until a clear solution was obtained, was added to a stirred boiling suspension of *N*-methyl-*o'p*-dinitrobenzanilide (8 g.) in alcohol (50 c.c.) and water (150 c.c.). After being boiled under reflux for 20 hours the mixture was cooled to 0° and the yellow solid which separated was collected. The filtrate was extracted with benzene and concentration of the dried (Na_2SO_4) extract gave a brown solid. The combined solids were recrystallised several times from benzene and gave p-*amino*-N-*methyl*-o'-*nitrobenzanilide* (6 g.) in orange needles, m. p. 148—149° (Found :

C, 62·6; H, 4·9. $C_{14}H_{13}O_3N_3$ requires C, 62·0; H, 4·8%). The application of the same procedure to *N*-methyl-*oo'*-dinitrobenzanilide (8 g.) gave on crystallisation from alcohol the unchanged *N*-methyldinitrobenzanilide (2·5 g.; m. p. 117—119° undepressed on admixture with the starting material), and on further concentration *o'-amino*-N-*methyl*-o-*nitrobenzanilide*, which separated from benzene–light petroleum (b. p. 80—100°) in orange plates (2 g.), m. p. 174—176° (Found: C, 62·0; H, 4·8%).

Preparation of N-*methyldinitrobenzanilides.*

Nitroaniline (g.)	Nitrobenzoic acid (g.)	Dinitrobenzanilide yield (g.)	m. p.	Dinitrobenzanilide taken (g.)	Me_2SO_4 (c.c.)	Acetone (c.c.)	20% NaOH (c.c.)	*N*-Methyldinitrobenzanilide yield (g.)	m. p.
o- 25	*p*- 25 *	2′:4- 29	222—223° [a]	24	50	100	100	22	126° [f]
o- 25	*m*- 25	2′:3- 38	137—138 [b]	36	75	150	150	28	110—111 [g]
o- 25	*o*- 25	2:2′- 33	155—157 [c]	30	50	125	125	26·5	124—125 [h]
m- 20	*o*- 20	2:3′- 26	192 [d]	16	50	70	70	16	137—138 [i]
p- 30	*o*- 30	2:4′- 34	210—212 [e]	30	70	120	120	30·5	149—150 [j]

* Acid chloride.

[a] Miklaszewski and Niementowski (*Ber.*, 1901, **34**, 2959) recorded m. p. 216°. [b] Witjens (*Rec. Trav. chim.*, 1943, **62**, 523) recorded m. p. 139—140°. [c] Niementowski (*Ber.*, 1899, **32**, 1463) recorded m. p. 167—168°, which fell to 133—136° on exposure to light. [d] Needles from benzene–acetone (Found: C, 54·5; H, 3·0. $C_{13}H_9O_5N_3$ requires C, 54·4; H, 3·2%). [e] Witjens (*loc. cit.*) recorded m. p. 219—220°. [f] Prisms from benzene–light petroleum (b. p. 80—100°) (Found: C, 56·2; H, 3·6. $C_{14}H_{11}O_5N_3$ requires C, 55·8; H, 3·8%). [g] Needles from aqueous alcohol (Found: C, 55·5; H, 3·6. $C_{14}H_{11}O_5N_3$ requires C, 55·8; H, 3·8%). [h] Prisms from benzene–light petroleum (b. p. 80—100°) (Found: C, 56·0; H, 3·6%). [i] Prisms from aqueous alcohol (Found: C, 56·0; H, 3·6%). [j] Plates from aqueous alcohol (Found: C, 56·0; H, 3·6%). (The dinitroanilides are pale yellow. The previous preparations were by different methods.)

Methylation of o′-*Nitrophthalanilic Acid.*—(*a*) Methyl sulphate (50 c.c.) was added slowly to a solution of *o'*-nitrophthalanilic acid (33 g.) (Meyer and Maier, *Annalen*, 1903, **327**, 55) in 10% aqueous sodium hydroxide (100 c.c.) at 70°. When the vigorous reaction had subsided the mixture was cooled by the addition of ice, and an excess of aqueous sodium hydroxide was added. The oil, which had separated, solidified and crystallisation from aqueous alcohol with charcoal gave *methyl* N-*methyl*-o′-*nitrophthalanilate* (10·7 g.) in yellow plates, m. p. 126—127° (Found: C, 61·1; H, 4·4. $C_{16}H_{14}O_5N_2$ requires C, 61·2; H, 4·5%). Crystallisation from benzene–light petroleum (b. p. 80—100°) gave yellow prisms, m. p. 127°. Acidification of the cold alkaline solution precipitated, overnight, N-*methyl*-o′-*nitrophthalanilic acid* (13·7 g.), which crystallised from alcohol in pale yellow prisms, m. p. 177° (Found: C, 60·3; H, 4·1. $C_{15}H_{12}O_5N_2$ requires C, 60·0; H, 4·0%). The ester was hydrolysed quantitatively to the acid by boiling it under reflux for 20 minutes with 4% aqueous sodium hydroxide. (*b*) In a second preparation conducted as above, but with *o'*-nitrophthalanilic acid (40 g.), 10% aqueous sodium hydroxide (150 c.c.), and methyl sulphate (100 c.c.), the products were methyl *N*-methyl-*o'*-nitrophthalanilate (30 g.), m. p. 126—127°, and *N*-methyl-*o'*-nitrophthalanilic acid (8 g.), m. p. 176—177°. (*c*) Methyl sulphate (4·5 c.c.) was shaken with a suspension of *o'*-nitrophthalanilic acid (10 g.) in 4% aqueous sodium hydroxide (100 c.c.) at room temperature for ½ hour. Acidification of the filtered solution gave *N*-methyl-*o'*-nitrophthalanilic acid (8·2 g.), pale yellow prisms (from aqueous alcohol), m. p. 175—176°.

N-*Methyl*-o′-*nitrophthalanilamide.*—A solution of *N*-methyl-*o'*-nitrophthalaniloyl chloride, prepared as a yellow gum from the acid (14 g.) by boiling thionyl chloride, in dry benzene (200 c.c.) at 0° was saturated with dry ammonia. The yellow solid which separated was filtered off and washed with water. The filtrate was washed with aqueous ammonia. The residue obtained on evaporation of the benzene solution was combined with the precipitate and crystallisation of the whole from ethyl alcohol gave N-*methyl*-o′-*nitrophthalanilamide* (12·5 g.) in yellow needles, m. p. 183—184° (Found: C, 60·5; H, 4·6. $C_{15}H_{13}O_4N_3$ requires C, 60·2; H, 4·7%).

N-*Methyl*-o′-*nitrophthalanilazide.*—Sodium azide (1·2 g.) in water (5 c.c.) was added with shaking to *N*-methyl-*o'*-nitrophthalaniloyl chloride (prepared as described above, from 5 g. of acid) in acetone (30 c.c.) at 0°. The mixture was shaken for 15 minutes and then poured into water (300 c.c.). The yellow oil, which separated, solidified. The solid was collected and washed with concentrated aqueous ammonia. N-*Methyl*-o′-*nitrophthalanilazide* (1 g.) was obtained as a yellow powder, m. p. 110—112° (decomp.) (Found: C, 55·5; H, 3·3. $C_{15}H_{11}O_4N_5$

requires C, 55·4; H, 3·4%). Acidification of the ammoniacal washings gave the unchanged acid (3 g.), m. p. 175—176°.

o-*Amino-N-methyl-o'-nitrobenzanilide.*—(a) *From N-methyl-o'-nitrophthalanilamide.* A suspension of the amide (5 g.) in a solution of bromine (8 g.) in 5·6% aqueous potassium hydroxide (200 c.c.) was stirred at 0° for 1 hour and then filtered. The orange-coloured filtrate was heated at 80° for 15 minutes, then extracted with ether. Evaporation of the solvent gave a red tar but subsequent crystallisation from benzene–light petroleum (b. p. 80—100°) gave o-*amino-N-methyl-o'-nitrobenzanilide* (1·5 g.) in orange plates, m. p. 104—105° (Found: C, 62·0; H, 4·9. $C_{14}H_{13}O_3N_3$ requires C, 62·0; H, 4·8%).

(b) *From N-methyl-o'-nitrophthalanilazide.* A suspension of the azide (1 g.) in dry benzene (40 c.c.) was heated on a steam-bath. The solid dissolved slowly with evolution of nitrogen, to give a yellow solution. The solution was boiled under reflux to complete the reaction. After the addition of 50% aqueous sodium hydroxide (40 c.c.) the mixture was boiled under reflux for a further 3 hours. The benzene layer was separated, dried (Na_2SO_4), and concentrated. *o*-Amino-*N*-methyl-*o'*-nitrobenzanilide (0·3 g.) separated in orange plates, m. p. 103—104°, undepressed on admixture with the specimen prepared by method (*a*) above.

N-Methyl-o-, N-Methyl-p-, and N-Methyl-3 : 5-di-nitroaniline.—*N*-Methyl-*o*-nitroaniline was prepared by Usherwood and Whiteley's method (*J.*, 1923, 1084). *N*-Methyl-*p*-nitroaniline was prepared by Halberkann's method (*Ber.*, 1921, **54**, 1833), with Usherwood and Whiteley's method for the hydrolysis of the methylsulphonanilide. 3 : 5-Dinitroaniline was prepared from 3 : 5-dinitrobenzoic acid according to Blanksma and Verberg (*Rec. Trav. chim.*, 1934, **53**, 988). A solution of 3 : 5-dinitroaniline (2 g.) and phthalic anhydride (3 g.) in ethyl acetate (30 c.c.) was boiled under reflux for 3 hours. 3 : 5-*Dinitrophthalanilic acid* (0·6 g.) separated and on recrystallisation from alcohol gave pale yellow plates, m. p. 208° (Found: C, 50·9; H, 2·7. $C_{14}H_9O_7N_3$ requires C, 50·6; H, 3·0%). To a solution of 3 : 5-dinitroaniline (28 g.) in pyridine (100 c.c.) toluene-*p*-sulphonyl chloride (26 g.) was slowly added. The solution was boiled for 5 minutes and poured into water. Crystallisation of the separated solid from acetic acid or alcohol gave 3 : 5-*dinitro-N-toluene*-p-*sulphonanilide* (20 g.), needles, m. p. 221—222° (Found: C, 46·0; H, 3·3. $C_{13}H_{11}O_6N_3S$ requires C, 46·3; H, 3·3%). Methyl sulphate (18 c.c.) was added with caution to a heated suspension of the sulphonanilide (20 g.) in 20% aqueous sodium hydroxide (100 c.c.). The mixture was kept alkaline and recrystallisation of the solid which separated gave N-*methyl*-3 : 5-*dinitro*-N-*toluene*-p-*sulphonanilide* (18 g.) in needles, m. p. 162° (Found: C, 48·2; H, 3·8. $C_{14}H_{13}O_6N_3S$ requires C, 47·9; H, 3·7%). A solution of this (18 g.) in concentrated sulphuric (30 c.c.) and acetic acid (15 c.c.) was heated on a steam-bath for 1 hour. When cold the mixture was poured into an excess of aqueous ammonia and ice. Crystallisation of the orange precipitate from methyl alcohol gave N-*methyl*-3 : 5-*dinitroaniline* (7·6 g.), orange plates, m. p. 158—159° (Found: C, 42·9; H, 3·6. $C_7H_7O_4N_3$ requires C, 42·6; H, 3·5%). Benzoylation (in boiling pyridine; 5 minutes) gave N-*methyl*-3′ : 5′-*dinitrobenzanilide*, pale yellow prisms, m. p. 124—125°, from benzene–light petroleum (b. p. 80—100°) (Found: C, 55·9; H, 3·7. $C_{14}H_{11}O_5N_3$ requires C, 55·8; H, 3·8%).

Preparation of o-*Amino*-N-*methylnitrobenzanilides* (cf. Schroeter and Eisleb, *loc. cit.*).—The *N*-methylnitroaniline and benzenesulphonylanthraniloyl chloride (Schroeter, *Ber.*, 1907, **40**, 1610) were boiled under reflux in benzene, after which the solvent was removed by distillation and the residual *o*-benzenesulphonamido-*N*-methylnitrobenzanilide crystallised. Subsequent hydrolysis was effected at room temperature in concentrated sulphuric acid for 4 or 5 days, after which the solution was poured slowly into an excess of ice and aqueous ammonia. The yellow solid which separated was adsorbed on alumina (20 × 2 cm.) from benzene or benzene–light petroleum (b. p. 60—80°) and elution with the same solvent gave the pure *o*-amino-*N*-methylnitrobenzanilide. The results obtained are summarised below:

o-*Benzenesulphonamido*-N-*methylnitrobenzanilides.*

N-Methylaniline: cpd.	g.	*N*-Benzenesulphonylanthraniloyl chloride (g.)	Time of reflux (hr.)	*o*-Benzenesulphonamido-*N*-methylnitrobenzanilide: g.	m. p.
o-Nitro	10	10	6	10	115—116° [a]
p-Nitro	6·5	11	20	13	170—171 [b]
3 : 5-Dinitro	7·6	10·8	44	12·8	190 [c]

[a] Pale yellow prisms from alcohol–light petroleum (b. p. 80—100°) (Found: C, 58·4; H, 4·0; N, 9·9. $C_{20}H_{17}O_5N_3S$ requires C, 58·4; H, 4·1; N, 10·1%). [b] Pale yellow prisms from benzene (Found: C, 58·5; H, 4·1; N, 9·8%). [c] Pale yellow prisms from aqueous acetic acid (Found: C, 52·8; H, 3·3; N, 12·0. $C_{20}H_{16}O_7N_4S$ requires C, 52·6; H, 3·3; N, 12·3%).

o-*Amino*-N-*methylnitrobenzanilides.*

o-Benzenesulphonamido-*N*-methylbenzanilide : cpd.	g.	Sulphuric acid (c.c.)	Time (days)	*o*-Amino-*N*-methylnitrobenzanilide : g.	m. p.
o'-Nitro	10	50	4	4·0	103—104° [d]
p'-Nitro	13	70	4	5·0	160—161 [e]
3′ : 5′-Dinitro	11	70	5	3·5	188—189 [f]

[d] 2·5 G. of unchanged starting material were recovered from the solution in benzene–light petroleum (b. p. 60—80°) (4 : 1) before adsorption. The product did not depress the m. p. of the compound prepared by Hofmann or Curtius degradation described above. [e] 2·5 G. of unchanged starting material were recovered from the solution in benzene–light petroleum (b. p. 60—80°) (3 : 1) before adsorption. The *product* separated from benzene–light petroleum (b. p. 80—100°) in yellow prisms (Found : C, 62·0; H, 4·9. $C_{14}H_{13}O_3N_3$ requires C, 62·0; H, 4·8%). [f] Elution was by benzene. The *product* separated from benzene in yellow needles (Found : C, 52·8; H, 3·6. $C_{14}H_{12}O_5N_4$ requires C, 53·2; H, 3·8%).

Decomposition of the Diazonium Fluoroborate prepared from p-*Amino*-N-*methyl*-o-*nitrobenzanilide.*—A suspension of this anilide (3 g.) in concentrated sulphuric acid (10 c.c.) and water (30 c.c.) was diazotised at 0° with a solution of sodium nitrite (1 g.) in water (10 c.c.). After being stirred for 1 hour at 0—5° the solution was filtered and sodium fluoroborate (5 g.) in water (10 c.c.) was added at 0°. The diazonium fluoroborate was collected, dried under reduced pressure, and suspended in " AnalaR " acetone (50 c.c.) to which copper powder (3 g.), prepared from zinc dust and aqueous copper sulphate, was added. On warming, nitrogen was freely evolved. When the reaction was complete, as shown by a negative coupling reaction with alkaline β-naphthol, the mixture was filtered into an excess of cold water. The residue was washed with boiling water and hot acetone, and the combined aqueous acetone solution was extracted with chloroform and the extract washed with 10% aqueous sodium hydroxide. Concentration of the dried (Na_2SO_4) neutral extract gave a red oil (3·2 g.), which was adsorbed from benzene–light petroleum (b. p. 60—80°) (3 : 1) on alumina (20 × 2 cm.). Elution with the same solvent (600 c.c.) and then with benzene (700 c.c.) gave *N*-methyl-*o'*-nitrobenzanilide (1·7 g.), which separated from benzene–light petroleum (b. p. 80—100°) in yellow needles, m. p. 81°, both alone and on admixture with an authentic specimen. Further elution gave a series of tars. Acidification of the alkaline washings and subsequent extraction with chloroform gave, on evaporation, p-*hydroxy*-N-*methyl*-o'-*nitrobenzanilide* (0·42 g.), which crystallised from methyl alcohol in yellow needles, m. p. 209° (Found : C, 62·2; H, 4·5; N, 10·1. $C_{14}H_{12}O_4N_2$ requires C, 61·8; H, 4·3; N, 10·3%).

Decomposition of the Diazonium Sulphate prepared from o-*Amino*-N-*methyl*-o'-*nitrobenzanilide.*—A solution of the *o*-amino-*N*-methyl-*o'*-nitrobenzanilide (2 g.) in sulphuric acid (7 c.c.) and water (100 c.c.) was diazotised at 0° with a solution of sodium nitrite (0·8 g.) in water (10 c.c.). After being stirred at 0° for 1 hour, the filtered solution was heated at 70° for 1 hour. Much tar was formed and the mixture was extracted with chloroform and the extract repeatedly washed with 10% aqueous sodium hydroxide. Evaporation of the dried (Na_2SO_4) chloroform solution gave a brown gum (1·0 g.), which was adsorbed from benzene on alumina (2 × 20 cm.). Elution with benzene (500 c.c.) gave 10-*methyl*-1-*nitrophenanthridone* (0·2 g.), which separated from light petroleum (b. p. 80—100°) in yellow needles, m. p. 92—93° (Found : C, 65·5; H, 4·2. $C_{14}H_{10}O_3N_2$ requires C, 66·1; H, 3·9%). Subsequent elution with benzene and then with benzene–ether (3 : 1) gave small quantities of yellow needles, m. p. 160—165° and colourless needles, m. p. 155—158° (mixed m. p. 135—142°). Acidification of the alkaline washings and extraction with chloroform gave on evaporation a brown tar (1·0 g.), which was adsorbed from benzene on silica gel (10 × 1 cm.). Elution with benzene (600 c.c.) gave o-*hydroxy*-N-*methyl*-o'-*nitrobenzanilide* (0·18 g.), yellow needles (from methyl alcohol), m. p. 157—158° (Found : C, 61·7; H, 4·2. $C_{14}H_{12}O_4N_2$ requires C, 61·8; H, 4·3%).

Decomposition of the Diazonium Fluoroborate prepared from o-*Amino*-N-*methyl*-o'-*nitrobenzanilide.*—The diazonium fluoroborate, prepared from the anilide (1·5 g.) as described above for the isomeric *p*-amino-compound, was allowed to decompose in " AnalaR " acetone (50 c.c.) with the addition of copper powder (2 g.). The reaction products were isolated and purified as described above. The neutral chloroform extract gave an orange-coloured solid (0·42 g.), which was adsorbed from benzene–light petroleum (b. p. 60—80°) (2 : 1) on alumina (2 × 20 cm.). Elution with the same solvent (400 c.c.) gave 10-methyl-1-nitrophenanthridone (0·3 g.), which crystallised from light petroleum (b. p. 80—100°) in yellow needles, m. p. 92—93°, undepressed on admixture with the compound prepared as above from decomposition of the diazonium sulphate in aqueous solution. Further elution afforded only orange-coloured

gums. The alkaline washings, on acidification, extraction, and evaporation, gave only a trace of a black tar.

Decomposition of the Diazonium Fluoroborate prepared from o-*Amino*-N-*methyl*-p′-*nitrobenzanilide.*—In similar manner this anilide (3·0 g.) was converted into the diazonium fluoroborate and decomposed. The neutral chloroform extract gave a dark-red solid (2·8 g.), which was purified by adsorption on alumina and afforded 10-*methyl*-3-*nitrophenanthridone* (0·8 g.), yellow needles (from benzene), m. p. 249° (Found : C, 66·0; H, 3·8%). Further elution of the column gave needles (0·4 g.), m. p. 178—180° (Found : C, 65·5; H, 4·5; N, 11·0%; *M*, 248). The alkaline washings yielded only a trace of a brown tar.

Decomposition of the Diazonium Fluoroborate prepared from o-*Amino*-N-*methyl*-3′ : 5′-*dinitrobenzanilide.*—This reaction was carried out as described for the preceding examples, but with *o*-amino-*N*-methyl-3 : 5-dinitrobenzanilide (3·2 g.) in sulphuric acid (10 c.c.) and water (100 c.c.). Five hours were allowed for the completion of the diazotisation. The neutral chloroform extract gave a red solid (1·7 g.), which on chromatographic purification afforded 10-*methyl*-2 : 4-*dinitrophenanthridone* (0·75 g.), yellow needles (from aqueous acetic acid), m. p. 281° (Found : C, 56·2; H, 3·1. $C_{14}H_9O_5N_3$ requires C, 56·2; H, 3·0%), and on further elution a second compound which crystallised from the same solvent in buff-coloured plates (0·5 g.), m. p. 244—246° (Found : C, 55·7; H, 3·3; N, 14·0%; *M*, 262). The alkaline extract afforded only a small quantity of a red tar.

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2. *Synthesis of Polymethylnaphthalenes.*

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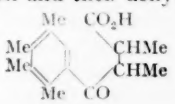
1 : 2 : 3 : 4-Tetramethylbenzene (prehnitene) was used as the starting point in the synthesis of 1 : 2 : 3 : 4 : 6-penta-, 1 : 2 : 3 : 4 : 5 : 6-, 1 : 2 : 3 : 4 : 5 : 7-, and 1 : 2 : 3 : 4 : 6 : 7-hexa-, and 1 : 2 : 3 : 4 : 5 : 6 : 7-hepta- and octa-methylnaphthalenes. With a large excess of maleic anhydride four of these hydrocarbons underwent Diels–Alder addition, yields ranging from 45 to 68%. Polymethylanthracenes were formed as by-products when tetrachloro-ethane was used as solvent in Friedel–Crafts condensations in which *p*-xylene or prehnitene formed one reactant. With *p*-xylene one of these by-products was probably 1 : 2 : 4-trimethylanthracene.

Very few fully substituted naphthalene derivatives are known. *peri*-Substituents in the naphthalene molecule are liable to overlap in the absence of molecular distortion, and it was thought that this effect might be accentuated in a completely substituted naphthalene. The primary purpose of the present investigation was the synthesis of octamethylnaphthalene for examination of its physical characteristics. This has been accomplished by several routes and *X*-ray crystallographic examination of the hydrocarbon has shown that the congestion of methyl groups is such as to produce actual distortion of the naphthalene rings (see following paper). Suitable modification of the synthetic procedures enabled us to prepare also a pentamethylnapthalene, three hexamethylnaphthalenes, and a heptamethylnaphthalene. Until recently the most highly methylated naphthalene described in the literature was a pentamethyl compound. Since our experiments were completed, Mosby (*J. Amer. Chem. Soc.*, 1952, **74**, 2564) recorded the synthesis of a new pentamethylnaphthalene and a new hexamethylnaphthalene.

The most satisfactory route to octamethylnaphthalene involved the intermediate formation of 1 : 2 : 3 : 4 : 5 : 6 : 7-heptamethylnaphthalene (III), which was converted into the 8-chloromethyl derivative and this submitted to catalytic hydrogenation over palladised charcoal, whereby octamethylnapthalene was formed (cf. Hewett, *J.*, 1940, 293). For the preparation of the heptamethylnaphthalene, prehnitene was condensed with αβ-dimethylsuccinic anhydride in presence of aluminium chloride to give γ-keto-αβ-dimethyl-γ-prehnitylbutyric acid (I). Hydrogenation of its sodium salt over copper chromite led to αβ-dimethyl-γ-prehnitylbutyric acid which was cyclised by hydrogen fluoride to 1 : 2 : 3 : 4-

tetrahydro-1-keto-2 : 3 : 5 : 6 : 7 : 8-hexamethylnaphthalene (II). This ketone reacted normally with methylmagnesium iodide and the resulting crude alcohol was submitted to dehydration and then dehydrogenation, giving the heptamethylnaphthalene (III).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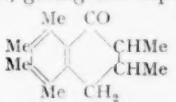
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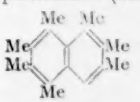
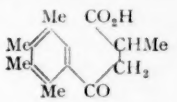
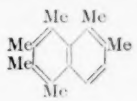

(III)

A possible variant of the above synthesis of octamethylnaphthalene would have involved introduction of one of the two final methyl groups at an earlier stage by treating the methyl ester of (I) with one molecular proportion of methylmagnesium iodide. Not unexpectedly, however, the carbonyl group proved too hindered for preferential attack by the Grignard reagent and no acidic product was formed after hydrolysis. Similar failure attended an attempt to condense methyl α-bromo-αβ-dimethylsuccinate with acetylprehnitene by the Reformatsky reaction. However, this ketone reacted with the usual carbonyl reagents.

Reduction of the tetrahydroketohexamethylnaphthalene (II) by Clemmensen's method or by the Huang-Minlon procedure gave, in poor yield, the corresponding tetrahydrohexamethylnaphthalene, and catalytic hydrogenation of (II) followed by dehydration gave a good yield of the corresponding dihydrohexamethylnaphthalene. Both these hydrocarbons were smoothly dehydrogenated to 1 : 2 : 3 : 4 : 6 : 7-hexamethylnaphthalene (XIII).

Prehnitene was condensed with methylsuccinic anhydride in presence of aluminium chloride to give in 85% yield the homogeneous γ-keto-α-methyl-γ-prehnitylbutyric acid (IV). This readily gave a 2 : 4-dinitrophenylhydrazone and was easily reduced by Clemmensen's method to α-methyl-γ-prehnitylbutyric acid. In both these respects the behaviour of the keto-acid (IV) was in marked contrast to that of its homologue (I), which supports the view that methylsuccinic anhydride had reacted to give the α-methylbutyric acid rather than the β-methyl acid. α-Methyl-γ-prehnitylbutyric acid was cyclised by hydrogen fluoride to 1 : 2 : 3 : 4-tetrahydro-1-keto-2 : 5 : 6 : 7 : 8-pentamethylnaphthalene, which was converted by standard reactions into 1 : 2 : 3 : 4 : 6-pentamethylnaphthalene and 1 : 2 : 3 : 4 : 5 : 6-hexamethylnaphthalene (V). The compound (VI) formed by addition of maleic anhydride to this hexamethylnaphthalene (see below) was oxidised to benzene-1 : 2 : 3 : 4-tetracarboxylic acid, which confirms the structures assigned to (IV) and (V). If the isomeric β-methylbutyric acid derivative had been formed this would have led to 1 : 2 : 3 : 4 : 5 : 7-hexamethylnaphthalene, the maleic anhydride adduct of which would have been oxidised to benzene-1 : 2 : 3 : 5-tetracarboxylic or to mellitic acid.


(IV)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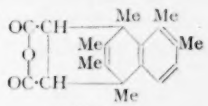
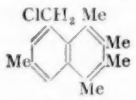
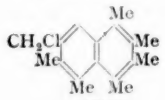

(VI)

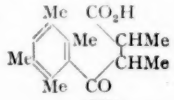
1 : 2 : 3 : 4 : 5 : 7-Hexamethylnaphthalene was, in fact, obtained from 1 : 2 : 3 : 4 : 6-pentamethylnaphthalene by chloromethylation to (VII) followed by catalytic dechlorination. The structure (VII) follows from the fact that the hexamethylnaphthalene formed from it was distinct from both 1 : 2 : 3 : 4 : 5 : 6- and 1 : 2 : 3 : 4 : 6 : 7-hexamethylnaphthalene. A fourth hexamethylnaphthalene (1 : 2 : 3 : 4 : 5 : 8-) has been described by Mosby (*loc. cit.*). The failure of 1 : 2 : 3 : 4 : 6-pentamethylnaphthalene to undergo chloromethylation at position 5, which would have been expected by analogy with simpler derivatives of 2-methylnaphthalene, is possibly due to the steric influence of the methyl group at position 4. It was hoped that 1 : 2 : 3 : 4 : 5 : 6-hexamethylnaphthalene also would undergo chloromethylation at position 8 to give a product which could be reduced to give a second heptamethylnaphthalene. Curiously, substitution took place at the alternative β-position to give (VIII) which was converted by catalytic dechlorination into 1 : 2 : 3 : 4 : 5 : 6 : 7-heptamethylnaphthalene.

In our earlier experiments on the synthesis of polymethylnaphthalenes αβ-dimethyl-

succinic anhydride was treated with durene. The acid (IX) was reduced to γ-duryl-αβ-dimethylbutyric acid, and this underwent rearrangement and cyclisation under the influence of hydrogen fluoride (cf. Badger, Carruthers, and Cook, *J.*, 1949, 2044; Aitken, Badger, and Cook, *J.*, 1950, 331) to produce the ketone (II) in 50% yield. The initial

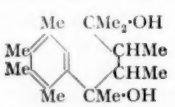

(VII)


(VIII)

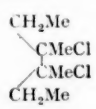

(IX)

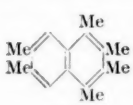
Friedel–Crafts reaction was complicated by the fact that methyl migration took place to some extent in this stage also, so that the γ-duryl acid (IX) was accompanied by about a quarter of its weight of the γ-prehnityl acid (I). These were separated by taking advantage of the sparing water-solubility of the sodium salt of the latter; their structures were shown by oxidation with sodium hypobromite and hydrolysis with hydrochloric acid in a sealed tube to the appropriate substituted benzoic acids and hydrocarbons respectively. In subsequent Friedel–Crafts reactions with αβ-dimethylsuccinic anhydride it was more convenient to use prehnitene, formed from a mixture of durene and *iso*durene by the Jacobsen reaction.

In another approach to the synthesis of octamethylnaphthalene methyl γ-keto-αβ-dimethyl-γ-prehnitylbutyrate (cf. I) was treated with excess of methylmagnesium iodide to give an oil which evidently contained the desired diol (X) as on treatment with hydrogen fluoride (cf. Kloetzel, *J. Amer. Chem. Soc.*, 1940, **62**, 3405) it gave a very small yield of octamethylnaphthalene (isolated through its complex with 2 : 4 : 7-trinitrofluorenone).


(X)

(XI)


(XII)


(XIII)

Bruson and Kroeger (*J. Amer. Chem. Soc.*, 1940, **62**, 36) have shown that ditertiary 1 : 4-diols, and also the 1 : 4-dichlorides and the conjugated dienes related to them, undergo a double condensation with aromatic compounds (" cycli-alkylation ") under the influence of aluminium chloride to give fused-ring hydroaromatic compounds. In all cases the dienes may well be intermediates and this probably applies also to the reaction of 3 : 4-dichloro-3 : 4-dimethylhexane (XII) with benzene, which was found by Sisido and Nozaki (*ibid.*, 1947, **69**, 961) to give 1 : 2 : 3 : 4-tetramethyltetralin. These reactions suggested yet another route to the higher polymethylnaphthalenes. Unfortunately, aluminium chloride caused loss and migration of methyl groups so that mixtures were formed. *o*-Xylene (XI) and (XII) gave 1 : 2 : 3 : 4 : 6 : 7-hexamethylnaphthalene (XIII), together with an oil from which was isolated, after selenium dehydrogenation, 1 : 2 : 3 : 4 : 5 : 7-hexamethylnaphthalene (cf. VII) (probably as a result of initial isomerisation of *o*- to *m*-xylene). Prehnitene reacted with 3 : 4-dichloro-3 : 4-dimethylhexane (XII) at 40° to give, after dehydrogenation, a mixture containing 1 : 2 : 3 : 4 : 6 : 7-hexamethyl-, 1 : 2 : 3 : 4 : 5 : 6 : 7-heptamethyl-, and octamethyl-naphthalene. Another experiment at 60° gave, in addition to the hepta- and octamethylnaphthalene, a hydrocarbon, m. p. 236°, having the ultra-violet absorption of an anthracene derivative and the composition of a hexamethylanthracene. Chromic acid oxidation gave a hexamethylanthraquinone, so that the *meso*-positions of the hydrocarbon are unsubstituted.

Condensation of *p*-xylene with 2 : 3 : 4 : 5-tetramethylhexane-2 : 5-diol gave as the only isolable solid product an anthracene hydrocarbon which, from its composition and m. p. (241°), and the m. p. of the quinone, appeared to be 1 : 2 : 4-trimethylanthracene. Probably the tetrachloroethane used as a solvent in the Friedel–Crafts reaction played a part in the formation of this hydrocarbon. A lower-boiling liquid fraction gave, after selenium dehydrogenation, a red picrate, m. p. 185°, which was also obtained under similar conditions from the condensation product of prehnitene with 2 : 5-dimethylhexane-2 : 5-

diol. The derived hydrocarbon, m. p. 125—128°, had the absorption characteristics of a polymethylnaphthalene. The prehnitene condensation also yielded an anthracene hydrocarbon, m. p. 236°, which has not been identified.

While this synthetic work was in progress Kloetzel, Dayton, and Herzog (*ibid.*, 1950, **72**, 273) reported that 1 : 2 : 3 : 4-tetramethylnaphthalene undergoes a Diels–Alder addition of maleic anhydride in the substituted ring, and with a large excess of the reagent they obtained a 90% yield of adduct. Lower homologues were subsequently found to give similar adducts, but in much smaller yield (Kloetzel and Herzog, *ibid.*, p. 1991).

It seemed of interest, therefore, to examine the behaviour of some of our polymethylnaphthalenes in this reaction. The hydrocarbon was heated in benzene solution with 30 mols. of maleic anhydride. Adducts were formed in all of the 5 cases investigated, and the figures in parentheses give the yield of adduct obtained after 48 hours : 1 : 2 : 3 : 4 : 6-pentamethyl (50%); 1 : 2 : 3 : 4 : 5 : 6-hexamethyl (68%); 1 : 2 : 3 : 4 : 6 : 7-hexamethyl (45%); 1 : 2 : 3 : 4 : 5 : 6 : 7-heptamethyl (60%); octamethyl (62%). In each case the hydrocarbon was regenerated quantitatively when the adduct was heated above its m. p. under reduced pressure. For the two hexamethylnaphthalenes it was shown that maleic anhydride had been added to the fully substituted ring, for the adduct (VI) from 1 : 2 : 3 : 4 : 5 : 6-hexamethylnaphthalene was oxidised by alkaline permanganate to prehnitic acid and that from 1 : 2 : 3 : 4 : 6 : 7-hexamethylnaphthalene to pyromellitic acid. The absorption spectra of the adducts had the expected benzenoid character.

Experimental

Light petroleum had b. p. 40—60°, ligroin b. p. 100—120°.

Condensation of αβ-Dimethylsuccinic Anhydride with Durene.—Durene was prepared by bischloromethylation of commercial xylene followed by reduction with zinc dust and sodium hydroxide (von Braun and Nelles, *Ber.*, 1934, **67**, 1094); (±)-αβ-dimethylsuccinic anhydride was obtained as described by Fieser and Daudt (*J. Amer. Chem. Soc.*, 1941, **63**, 782). Durene (3·3 g.) and αβ-dimethylsuccinic anhydride were added in small portions, during 40 minutes, to a stirred ice-cold suspension of powdered anhydrous aluminium chloride (10 g.) in carbon disulphide (70 c.c.). Stirring was continued for 4 hours and the reaction mixture kept at room temperature overnight. The solvent was decanted and the residue decomposed with ice and hydrochloric acid. The resinous product was boiled with sodium carbonate solution and extracted with ether to remove surplus durene. The aqueous solution was evaporated to 15 c.c. and kept in the refrigerator overnight. A sparingly soluble sodium salt (0·8 g.) separated. Acidification of this gave *γ-keto-αβ-dimethyl-γ-prehnitylbutyric acid* (I) which crystallised from benzene–light petroleum in needles, m. p. 151—152° (Found : C, 73·6; H, 8·55. $C_{16}H_{22}O_3$ requires C, 73·3; H, 8·4%). The *methyl* ester (prepared with methanol and sulphuric acid) formed plates (from methanol), m. p. 88° (Found : C, 73·6; H, 8·85. $C_{17}H_{24}O_3$ requires C, 73·9; H, 8·7%).

A solution of the acid (100 mg.) in acetic acid (3 c.c.) and acetic anhydride (0·2 c.c.) was saturated with hydrogen chloride, then kept overnight, and evaporated, and the residue twice evaporated with benzene. The resulting unsaturated *lactone* formed needles (from benzene–light petroleum), m. p. 114·5° (Found : C, 78·7; H, 7·9. $C_{16}H_{20}O_2$ requires C, 78·65; H, 8·2%). The same lactone was formed when a solution of the acid in hydrogen fluoride was kept for 30 hours.

The alkaline filtrate from which the sodium salt of (I) had separated was acidified. The precipitate (2·4 g.) crystallised from dioxan to give thick needles, m. p. 147—148°, of *γ-duryl-γ-keto-αβ-dimethylbutyric acid* (IX) (Found : C, 73·7; H, 8·7. $C_{16}H_{22}O_3$ requires C, 73·3; H, 8·4%). Its *methyl* ester formed prisms (from methanol), m. p. 103° (Found : C, 73·85; H, 8·5%), and the acid was converted by hydrogen chloride and acetic anhydride in acetic acid into the corresponding unsaturated lactone, m. p. 119° (Found : C, 78·8; H, 7·8. $C_{16}H_{20}O_2$ requires C, 78·65; H, 8·0%).

The same two acids (60% yield) were obtained when the Friedel–Crafts reaction was carried out in cold tetrachloroethane. The proportion of (IX) to (I) was then 10 : 1.

Structures of the Acids (I) *and* (IX).—(*a*) A solution of the acid (200 mg.) in ice-cold 10% sodium hypobromite (20 c.c.) was heated slowly to 100°, and the temperature kept thereat for 4 hours. The product, isolated as usual, was crystallised from ligroin. (I) thus gave 2 : 3 : 4 : 5-tetramethylbenzoic acid, m. p. 166—168° alone or mixed with an authentic specimen (lit., 169°);

the amide had m. p. 220° (lit., 222°). The acid (IX) similarly gave 2 : 3 : 5 : 6-tetramethylbenzoic acid, m. p. 176—178°, not depressed by an authentic specimen (lit., 179°).

(*b*) The acid (500 mg.) was heated in a sealed tube with concentrated hydrochloric acid for 5 hours at 150°. The acid (I) gave prehnitene, b. p. 202°/760 mm. (lit., 204°), whereas (IX) gave durene, m. p. and mixed m. p. 79—80° (from methanol).

5-*Acetylprehnitene*.—A mixture of durene and *iso*durene (Smith, *Org. Synth.*, 1930, **10**, 32) was converted into prehnitene by the Jacobsen reaction (Smith and Lux, *J. Amer. Chem. Soc.*, 1929, **51**, 2994; Smith and Cass, *ibid.*, 1932, **54**, 1614). 5-Acetylprehnitene, prepared by the Friedel–Crafts reaction with acetyl chloride, formed a yellow oil, b. p. 145°/15 mm. (cf. Claus and Föhlisch, *J. pr. Chem.*, 1888, **38**, 231). It gave an orange 2 : 4-*dinitrophenylhydrazone*, m. p. 155—156° (Found : N, 15·4. $C_{18}H_{20}O_4N_4$ requires N, 15·7%), an *oxime*, m. p. 122° (Found : N, 7·0. $C_{12}H_{17}ON$ requires N, 7·3%), and a *semicarbazone*, m. p. 203° (Found : N, 18·2. $C_{13}H_{19}ON_3$ requires N, 18·0%).

Condensation of αβ-Dimethylsuccinic Anhydride with Prehnitene.—Prehnitene (16·5 g.) and freshly powdered anhydrous aluminium chloride (50 g.) were added during an hour to an ice-cold stirred mixture of (±)-αβ-dimethylsuccinic anhydride (16 g.) and tetrachloroethane (120 c.c.). Stirring was continued for 6 hours. Next morning, the reaction mixture was treated with ice and hydrochloric acid, and steam-volatile material removed. The resinous residue was extracted with sodium carbonate solution and the filtered solution acidified. The resinous precipitate, which gradually solidified (m. p. 140—160°; 29 g.), was separated by fractional crystallisation from mixtures of various proportions of benzene and light petroleum into 2 stereoisomers (cf. Fieser and Daudt, *loc. cit.*). The principal component was γ-keto-αβ-dimethyl-α-prehnitylbutyric acid, m. p. 151—152°, described above (Found : C, 73·0; H, 8·2%). The isomeric *acid* formed small plates, m. p. 167—168° (Found : C, 73·4; H, 8·3%). For the subsequent stages the crude mixture, m. p. 140—160°, was used.

αβ-*Dimethyl-γ-prehnitylbutyric Acid*.—Attempted reduction of the keto-acid (I) by Clemmensen's method led to its recovery unchanged. A solution of the sodium salt of the acid (10 g.) in water (150 c.c.) was stirred and heated with copper chromite catalyst (6 g.) and hydrogen in a steel autoclave. The initial pressure at 140° was 130 atm. The temperature was slowly raised to 240° and kept thereat for 15 hours. The still warm solution was filtered from catalyst, evaporated to 50 c.c., and kept in the refrigerator overnight. The sodium salts which crystallised were redissolved in water, the solution acidified, and the precipitate extracted twice with ether (50 c.c.). The undissolved αβ-*dimethyl-γ-prehnitylbutyrolactone* (0·6 g.), which was insoluble in sodium carbonate solution, crystallised from methanol in prisms, m. p. 131—132° (Found : C, 77·85; H, 9·1. $C_{16}H_{22}O_2$ requires C, 78·1; H, 8·9%). Evaporation of the ethereal extract gave αβ-*dimethyl-γ-prehnitylbutyric acid* (6 g.) which crystallised from benzene in rosettes of needles, m. p. 135—136° (Found : C, 77·2; H, 9·6. $C_{16}H_{24}O_2$ requires C, 77·4; H, 9·7%). The original aqueous filtrate gave on acidification unchanged keto-acid (1 g.) of m. p. (165—166°) corresponding with that of the higher-melting component of the mixture. There was no depression on mixing.

1 : 2 : 3 : 4-*Tetrahydro*-1-*keto*-2 : 3 : 5 : 6 : 7 : 8-*hexamethylnaphthalene* (II).—(*a*) A solution of dimethylprehnitylbutyric acid (3 g.) in hydrogen fluoride (70 c.c.) was kept for 30 hours. The neutral product, freed from acidic material, distilled at 180°/4 mm. (2·4 g.). This *ketone* (II) crystallised from ligroin in stout needles, m. p. 120° (Found : C, 83·2; H, 9·3. $C_{16}H_{22}O$ requires C, 83·4; H, 9·55%).

(*b*) The same acid (3 g.) was converted into its chloride by treatment with phosphorus pentachloride (3 g.) in benzene (10 c.c.) followed after addition of the pentachloride by a further 30 c.c. Volatile material was removed at 60—70° under reduced pressure, and evaporation with benzene was thrice repeated. A solution of the residual acid chloride in dry benzene (20 c.c.) was added dropwise to a stirred suspension of aluminium chloride (35 g.) in benzene (50 c.c.). After 5 hours' stirring the complex was decomposed with ice and hydrochloric acid. The resulting ketone (II) (2 g.), crystallised from light petroleum, had m. p. 120°, undepressed by a sample prepared as described under (*a*). The ketone was oxidised with dilute nitric acid (1 part of conc. acid, 1 part of water) in a sealed tube at 175° to mellitic acid, identified by preparation of its methyl ester, m. p. 184—186° alone or mixed with an authentic sample.

5 : 6-*Dihydro*-1 : 2 : 3 : 4 : 6 : 7-*hexamethylnaphthalene*.—A solution of the aforesaid ketone (1 g.) in acetic acid (30 c.c.) was hydrogenated over Adams's platinum catalyst (2 hours). The crude alcohol was dehydrated by treatment with formic acid (2 hours at room temperature) or by distillation (200°/4 mm.), and the resulting hydrocarbon purified by passage of its solution in benzene–light petroleum through a column of alumina. 5 : 6-*Dihydro*-1 : 2 : 3 : 4 : 6 : 7-

hexamethylnaphthalene formed needles (0·7 g.) (from methanol), m. p. 117°, depressed to 104° by admixture with the tetrahydro-compound (below) (Found : C, 89·4; H, 10·3. $C_{16}H_{22}$ requires C, 89·65; H, 10·35%).

5 : 6 : 7 : 8-*Tetrahydro*-1 : 2 : 3 : 4 : 6 : 7-*hexamethylnaphthalene*.—(*a*) A mixture of the ketone (II) (0·5 g.), amalgamated zinc (5 g.), concentrated hydrochloric acid (25 c.c.), toluene (4 c.c.), and ethanol (1 c.c.) was boiled for 36 hours. More amalgamated zinc (2 g.) and hydrochloric acid (5 c.c.) were then added and boiling continued for 12 hours more. The product, recovered by ether-extraction, gave needles (0·1 g.) (from methanol) of **5 : 6 : 7 : 8-*tetrahydro*-1 : 2 : 3 : 4 : 6 : 7-*hexamethylnaphthalene***, m. p. 111° (Found : C, 88·9; H, 10·95. $C_{16}H_{24}$ requires C, 88·8; H, 11·2%).

(*b*) Reduction of the ketone (II) (0·5 g.) by the Huang-Minlon procedure gave the same hydrocarbon (0·3 g.).

1 : 2 : 3 : 4 : 6 : 7-*Hexamethylnaphthalene* (XIII).—This was obtained by dehydrogenation with 20% palladised charcoal of the dihydride at 200—220° or the tetrahydride at 250—300°. Purification by formation and dissociation of the picrate gave **1 : 2 : 3 : 4 : 6 : 7-*hexamethylnaphthalene*** as leaflets (from methanol), m. p. 145° (Found : C, 90·6; H, 9·5. $C_{16}H_{20}$ requires C, 90·5; H, 9·5%). The *picrate* formed dark red needles (from methanol), m. p. 190·5° Found : N, 9·8. $C_{16}H_{20},C_6H_3O_7N_3$ requires N, 9·5%); the *s*-trinitrobenzene *complex* formed orange needles (from methanol), m. p. 215° (Found : N, 9·9; $C_{16}H_{20},C_6H_3O_6N_3$ requires N, 9·9%); and the 2 : 4 : 7-trinitrofluorenone *complex* formed deep brick-red needles (from acetic acid), m. p. 210° (Found : N, 8·4. $C_{16}H_{20},C_{13}H_5O_7N_3$ requires N, 8·0%).

1 : 2 : 3 : 4 : 5 : 6 : 7-*Heptamethylnaphthalene*.—A solution of 1 : 2 : 3 : 4-tetrahydro-1-keto-2 : 3 : 5 : 6 : 7 : 8-hexamethylnaphthalene (II) (0·9 g.) in dry ether (20 c.c.) was added to a Grignard solution from methyl iodide (3·5 g.), magnesium turnings (0·6 g.), and ether (40 c.c.). The ether was removed and replaced by pure benzene (30 c.c.), and the solution boiled for 36 hours. The mixture was decomposed with ammonium chloride solution, the crude alcohol dehydrated with formic acid at room temperature and the liquid product (distilled at 170°/2 mm.) (0·6 g.) dehydrogenated by palladised charcoal in boiling trichlorobenzene (2 hours). The resulting **1 : 2 : 3 : 4 : 5 : 6 : 7-*heptamethylnaphthalene***, purified through its picrate, formed needles (from benzene–methanol), m. p. 134° (Found : C, 90·0; H, 9·5. $C_{17}H_{22}$ requires C, 90·2; H, 9·8%). Its dark brown *picrate* had m. p. 184·5° (Found : N, 9·5. $C_{17}H_{22},C_6H_3O_7N_3$ requires N, 9·5%); its orange-red *s*-trinitrobenzene *complex*, m. p. 210° (Found : N, 9·55. $C_{17}H_{22},C_6H_3O_6N_3$ requires N, 9·5%); its dark red *styphnate* (from methanol), m. p. 168° (Found : N, 9·1. $C_{17}H_{22},C_6H_3O_8N_3$ requires N, 8·9%); and its brownish-black 2 : 4 : 7-trinitrofluorenone *complex*, m. p. 212° (Found : N, 7·5. $C_{17}H_{22},C_{13}H_5O_7N_3$ requires N, 7·75%).

Octamethylnaphthalene.—(*a*) Hydrogen chloride was passed into a suspension of paraformaldehyde (0·1 g.) in acetic acid (3 c.c.) until dissolution was complete. The heptamethylnaphthalene (0·3 g.) was then added and the suspension shaken for 24 hours. More hydrogen chloride was led in and shaking continued for a further 24 hours. Ice was added, and the product extracted with ether. The extract was washed with sodium hydrogen carbonate solution and dried and the ether distilled off. The residual oil, which could not be distilled without decomposition, did not crystallise. Nevertheless, it was substantially 8-chloromethyl-1 : 2 : 3 : 4 : 5 : 6 : 7-heptamethylnaphthalene, of which it gave the *s*-trinitrobenzene *complex* as dark red needles, m. p. 160° (decomp.), when the components were mixed in hot benzene solution (Found : N, 8·8. $C_{18}H_{23}Cl,C_6H_3O_6N_3$ requires N, 8·6%).

A solution of the crude chloromethylheptamethylnaphthalene (0·1 g.) in *cyclo*hexane (15 c.c.) was shaken with hydrogen and 20% palladised charcoal (50 mg.) for ½ hour. The filtered solution was evaporated and the residue treated with picric acid in hot methanol. The recrystallised picrate was passed in benzene through a column of alumina. The ***octamethylnaphthalene***, obtained in this way free from the strongly adsorbed picric acid, crystallised from benzene–light petroleum in elongated plates (25 mg.) with a greenish tinge and had m. p. 174° (Found : C, 89·9; H, 10·2. $C_{18}H_{24}$ requires C, 89·9; H, 10·1%). The *picrate* formed almost black needles, m. p. 193°, after previous softening (Found : N, 9·1. $C_{18}H_{24},C_6H_3O_7N_3$ requires N, 8·9%); the *s*-trinitrobenzene *complex* formed dark red prisms (from benzene), m. p. 192—193° (Found : C, 63·5; H, 6·2. $C_{18}H_{24},C_6H_3O_6N_3$ requires C, 63·6; H, 6·1%); and the black 2 : 4 : 7-trinitrofluorenone *complex* (from acetic acid) had m. p. 209° (Found : N, 7·7. $C_{18}H_{24},C_{13}H_5O_7N_3$ requires N, 7·6%).

(*b*) Methyl γ-keto-αβ-dimethyl-γ-prehnitylbutyrate (2 g.) was added to a large excess of methylmagnesium iodide, and the mixture (with ether replaced by benzene) boiled for 60 hours. The magnesium complex was decomposed with ammonium chloride solution, and the ethereal

layer evaporated. The resulting oil (1·5 g.) was added to hydrogen fluoride (40 c.c.), and the solution kept for 36 hours. The product, dissolved in acetic acid, was treated with 2 : 4 : 7-trinitrofluorenone. The black crystalline complex (30 mg.) had m. p. 207—209°, and from this was regenerated, by reduction with stannous chloride in hydrochloric acid and acetic acid, octamethylnaphthalene (5 mg.), m. p. 172—173°, not depressed by admixture with a sample prepared as under (*a*). The *s*-trinitrobenzene complex had m. p. 192—193°. A further quantity (6 mg.) of octamethyl naphthalene was obtained by selenium dehydrogenation of the oil recovered from the mother-liquors from which the trinitrofluorenone complex had been obtained.

Condensation of Methylsuccinic Anhydride with Prehnitene.—Prehnitene (12 g.) was slowly added to a stirred ice-cold suspension of anhydrous aluminium chloride (40·5 g.) and methylsuccinic anhydride (10 g.) (Dev and Guha, *J. Indian Chem. Soc.*, 1948, **25**, 13) in tetrachloroethane (100 c.c.). Stirring at 0° was continued for 5 hours; the reaction mixture was treated with ice and hydrochloric acid, and the solvent removed in steam. The residue was extracted with sodium carbonate solution, and the filtered solution acidified. The precipitated gum soon became solid (18 g.). Crystallisation from benzene gave *γ-keto-α-methyl-γ-prehnitylbutyric acid* (IV) as prisms, m. p. 130—131° (Found : C, 72·55; H, 8·1. $C_{15}H_{20}O_3$ requires C, 72·55; H, 8·1%). The *ethyl* ester, obtained with ethanol and sulphuric acid, crystallised from ethanol in short rods, m. p. 68·5° (Found : C, 73·5; H, 8·9. $C_{12}H_{22}O_3$ requires C, 73·8; H, 8·8%), and gave on hydrolysis the keto-acid of unchanged m. p. Oxidation of the acid with sodium hypobromite, as described above for the homologue, gave prehnitenecarboxylic acid, m. p. 165—168°, from which was prepared the amide, m. p. and mixed m. p. 220—222°.

α-Methyl-γ-prehnitylbutyric Acid.—This was obtained in 85% yield by reduction of the keto-acid (IV), by using Martin's modification of the Clemmensen method. It formed leaflets (from methanol), m. p. 106—107° (Found : C, 76·6; H, 9·6. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%).

1 : 2 : 3 : 4-*Tetrahydro*-1-*keto*-2 : 5 : 6 : 7 : 8-*pentamethylnaphthalene.*—This was obtained by cyclisation of the aforesaid acid with hydrogen fluoride (in 83% yield) or by the action of aluminium chloride on the acid chloride (in 75% yield). The *ketone* formed small needles (from ligroin), m. p. 78·5° (Found : C, 83·2; H, 9·2. $C_{15}H_{20}O$ requires C, 83·4; H, 9·3%). It was oxidised by dilute nitric acid in a sealed tube to mellitic acid, identified as its methyl ester, m. p. 186°.

1 : 2 : 3 : 4 : 6-*Pentamethylnaphthalene.*—The cyclic ketone (1·2 g.) described in the preceding paragraph was hydrogenated in acetic acid over Adams's platinum catalyst, and the crude alcohol dehydrated with formic acid to give, after chromatographic purification, 7 : 8-*dihydro*-1 : 2 : 3 : 4 : 6-*pentamethylnaphthalene* which formed needles (0·63 g.) (from methanol), m. p. 64° (Found : C, 89·7; H, 10·1. $C_{15}H_{20}$ requires C, 89·9; H, 10·1%). This was dehydrogenated by 20% palladised charcoal at 200—220° (2 hours) to 1 : 2 : 3 : 4 : 6-*pentamethylnaphthalene* which formed rhombohedra (from methanol), m. p. 85° (Found : C, 90·7; H, 9·35. $C_{15}H_{18}$ requires C, 90·85; H, 9·15%). Its light red *picrate* had m. p. 176° (Found : N, 10·0. $C_{15}H_{18},C_6H_3O_7N_3$ requires N, 9·8%); its yellow *s*-trinitrobenzene *complex*, m. p. 187° (Found : N, 10·0. $C_{15}H_{18},C_6H_3O_6N_3$ requires N, 10·2%); and its red 2 : 4 : 7-trinitrofluorenone *complex*, m. p. 174° (Found : N, 8·4. $C_{15}H_{18},C_{13}H_5O_7N_3$ requires N, 8·2%).

1 : 2 : 3 : 4 : 5 : 6-*Hexamethylnaphthalene* (V).—1 : 2 : 3 : 4-Tetrahydro-1-keto-2 : 5 : 6 : 7 : 8-pentamethylnaphthalene was treated with excess of methylmagnesium iodide as described above for an analogous case. The oil, b. p. 170°/4 mm., obtained by dehydration of the crude alcohol was dehydrogenated by 20% palladised charcoal in boiling trichlorobenzene (2 hours). The resulting 1 : 2 : 3 : 4 : 5 : 6-*hexamethylnaphthalene*, purified through its picrate, formed needles (from methanol), m. p. 81·5° (Found : C, 90·3; H, 9·4. $C_{16}H_{20}$ requires C, 90·5; H, 9·5%). Its dark red *picrate* had m. p. 167—168° (Found : N, 9·6. $C_{16}H_{20},C_6H_3O_7N_3$ requires N, 9·5%); its orange *s*-trinitrobenzene *complex*, m. p. 186° (Found : N, 9·8. $C_{16}H_{20},C_6H_3O_6N_3$ requires N, 9·9%); and its 2 : 4 : 7-trinitrofluorenone *complex*, m. p. 181° (Found : N, 7·8. $C_{16}H_{20},C_{13}H_5O_7N_3$ requires N, 8·0%).

1 : 2 : 3 : 4 : 5 : 7-*Hexamethylnaphthalene.*—1 : 2 : 3 : 4 : 6-Pentamethylnaphthalene was chloromethylated as described for the heptamethylnaphthalene (III). The crude chloromethyl compound (VII), an oil which rapidly became coloured, was dechlorinated when its *cyclo*hexane solution was shaken with hydrogen and palladised charcoal. Purification through the picrate then gave 1 : 2 : 3 : 4 : 5 : 7-*hexamethylnaphthalene* as cubes (from methanol), m. p. 140° (Found : C, 90·45; H, 9·45%). Its m. p. was depressed by admixture with 1 : 2 : 3 : 4 : 6 : 7-hexamethylnaphthalene. The dark red *picrate* had m. p. 188° (Found : N, 9·75%); the *s*-trinitro-

benzene *complex*, m. p. 207° (Found : N, 9·9%); and the 2 : 4 : 7-trinitrofluorenone *complex*, m. p. 199° (Found : N, 7·85%).

1 : 2 : 3 : 4 : 5 : 6 : 7-*Heptamethylnaphthalene from* 1 : 2 : 3 : 4 : 5 : 6-*Hexamethylnaphthalene*. —The hexamethylnaphthalene was chloromethylated to give a liquid chloromethyl compound (VIII) characterised as its dark red *picrate*, m. p. 178—180° (decomp.) (Found : N, 8·9. $C_{17}H_{21}Cl,C_6H_3O_7N_3$ requires N, 8·6%), and its red *s*-trinitrobenzene *complex*, m. p. 188° (decomp.) (Found : N, 9·1. $C_{17}H_{21}Cl,C_6H_3O_6N_3$ requires N, 8·9%). The oil was submitted to catalytic hydrogenation over palladised charcoal and gave 1 : 2 : 3 : 4 : 5 : 6 : 7-heptamethylnaphthalene, m. p. 134° (picrate, m. p. 184·5°; 2 : 4 : 7-trinitrofluorenone complex, m. p. 212°). In all three cases there was no depression on admixture with samples prepared as described above.

Condensation of o-*Xylene with* 3 : 4-*Dichloro*-3 : 4-*dimethylhexane*.—3 : 4-Dichloro-3 : 4-dimethylhexane (18 g.) (Sisido and Nozaki, *loc. cit.*) was added during 2 hours to a stirred mixture of *o*-xylene (80 g.) and anhydrous aluminium chloride (10 g.). The temperature was then raised to 40° and kept thereat for 6 hours, after which the reaction mixture was kept overnight at room temperature and then decomposed with ice and hydrochloric acid. Unchanged reactants were distilled off and the residual oil fractionated at 8 mm. into (i) b. p. 110—130° (5 g.), (ii) b. p. 130—150° (10 g.), and (iii) b. p. 150—170° (7 g.). Fraction (ii) gave, after being heated with selenium, the 2 : 4 : 7-trinitrofluorenone complex of 1 : 2 : 3 : 4 : 5 : 7-hexamethylnaphthalene (40 mg.) from which the impure hydrocarbon (m. p. 133—135°) was recovered by reduction with stannous chloride, and further characterised by preparation of the picrate, m. p. 187—188°. Mixed m. p.s with authentic specimens showed no depression. Fraction (iii) deposited crystals which, after recrystallisation from ligroin and then methanol, had m. p. 145° (300 mg.) and were shown by mixed m. p. and the preparation of the picrate and the 2 : 4 : 7-trinitrofluorenone complex to consist of 1 : 2 : 3 : 4 : 6 : 7-hexamethylnaphthalene (Found : C, 90·1; H, 9·75%).

Condensation of Prehnitene with 3 : 4-*Dichloro*-3 : 4-*dimethylhexane*.—(a) *At* 35—40°. 3 : 4-Dichloro-3 : 4-dimethylhexane (15 g.) was added during 2 hours to a mixture of prehnitene (10 g.) and anhydrous aluminium chloride (10 g.). The temperature was raised to 40° and kept at 35—40° for 5 hours. The complex was decomposed in the usual way and unchanged reactants removed. The residue (8 g.) was heated with selenium (8 g.) in a sealed tube at 340° for 24 hours, and the product fractionated at 2 mm. in 4 fractions : (i) b. p. 110—130° (2 g.); (ii) b. p. 130—150° (1·5 g.); (iii) b. p. 150—160° (1 g.); and (iv) b. p. above 160° (0·5 g.). Fraction (ii) gave a red picrate, m. p. 140—141° (40 mg.), which was dissociated into 1 : 2 : 3 : 4 : 6 : 7-hexamethylnaphthalene, m. p. 144—145°. Fraction (iii) gave a brownish-black complex (50 mg.), m. p. 210—212°, with 2 : 4 : 7-trinitrofluorenone, which on dissociation gave 1 : 2 : 3 : 4 : 5 : 6 : 7-heptamethylnaphthalene, m. p. 132—133°. Fraction (iv) gave a 2 : 4 : 7-trinitrofluorenone complex (10 mg.), m. p. 207—209°, which was dissociated into octamethylnaphthalene, m. p. 171—173°. In all cases mixed m. p. determinations were made.

(b) *At* 60°. The conditions were as under (a) except that the reaction was carried out at 60° for 7 hours and then at 35—40° for 12 hours, and the selenium treatment was omitted. Fractionation at 1 mm. gave fractions : (i) b. p. 110—130° (2·5 g.); (ii) b. p. 130—150° (2 g.); (iii) b. p. 150—170° (0·7 g.); and (iv) b. p. above 170° (2 g.). Fraction (ii) formed a red picrate, m. p. 184—185° (20 mg.), dissociated to 1 : 2 : 3 : 4 : 5 : 6 : 7-heptamethylnaphthalene. Fraction (iii) gave a black 2 : 4 : 7-trinitrofluorenone complex (30 mg.), dissociated to octamethylnaphthalene. Fraction (iv) deposited crystals which after recrystallisation from benzene formed colourless leaflets, m. p. 236—237°, with the composition of a *hexamethylanthracene* (Found : C, 91·5; H, 8·5. $C_{20}H_{22}$ requires C, 91·5; H, 8·5%). The black *picrate* (from methanol) had m. p. 214° (Found : N, 8·7. $C_{20}H_{22},C_6H_3O_7N_3$ requires N, 8·6%); a red *s*-trinitrobenzene *complex* (from benzene), m. p. 224° (Found : N, 8·85. $C_{20}H_{22},C_6H_3O_6N_3$ requires N, 9·0%); and a brownish-black 2 : 4 : 7-trinitrofluorenone *complex*, m. p. 228° (Found : N, 7·4. $C_{20}H_{22},C_{13}H_5O_7N_3$ requires N, 7·3%). Oxidation of the hydrocarbon with chromic acid in acetic acid gave a *hexamethylanthraquinone*, m. p. 199° (Found : C, 82·9; H, 7·4. $C_{20}H_{20}O_2$ requires C, 82·2; H, 6·9%). The ultra-violet absorption spectrum of the hydrocarbon in ethanol showed clearly an anthracenoid character (maxima at 3930, 3730, 3610, and 3560 Å, with a more intense peak at 2680 Å).

Condensation of p-*Xylene with* 2 : 3 : 4 : 5-*Tetramethylhexane*-2 : 5-*diol*.—The dihydroxy-compound (1·5 g.) (Bruson and Kroeger, *loc. cit.*) was added during 10 minutes to a stirred mixture of tetrachloroethane (15 c.c.), *p*-xylene (4 g.), and anhydrous aluminium chloride (5 g.). The bath-temperature was then raised to 60° and kept there for 5 hours. The mixture was

worked up in the usual way and the solvent-free products distilled at 2 mm. The lower fraction, b. p. 140—160° (0·5 g.), was heated with selenium (0·5 g.) in a sealed tube at 330° for 24 hours. Treatment with methanolic picric acid then gave a deep red picrate (8 mg.), m. p. 182—185°, which was dissociated to give a colourless solid, m. p. 125—130°. The higher fraction, b. p. 200°, was semi-solid and after recrystallisation from benzene–ligroin and then benzene, formed yellowish leaflets, m. p. 241—242°, with a strong blue fluorescence in benzene (Found: C, 92·7; H, 7·65. Calc. for $C_{17}H_{16}$: C, 92·7; H, 7·3%). The ultra-violet absorption in ethanol was that of an anthracene derivative and the composition suggests a trimethylanthracene. It is not 1 : 2 : 3 : 4-tetramethylanthracene, which has m. p. 136° (Hewett, *loc. cit.*). The hydrocarbon gave a red *s*-trinitrobenzene complex, m. p. 146—148°, and a brownish-black 2 : 4 : 7-trinitrofluorenone complex, m. p. 160—162°, and was oxidised by chromic acid in acetic acid to a yellow quinone, m. p. 155—158°. 1 : 2 : 4-Trimethylanthracene has m. p. 244° and the quinone, m. p. 162—163° (Elbs, *J. pr. Chem.*, 1890, **41**, 121).

Condensation of Prehnitene with 2 : 3 : 4 : 5-*Tetramethylhexane*-2 : 5-*diol.*—Prehnitene (2·3 g.) was treated with the diol (2 g.) and aluminium chloride (8 g.) in tetrachloroethane (20 c.c.) as described for the reaction with *p*-xylene. Distillation of the product at 2 mm. gave (*a*) an oil, b. p. 130—150° (0·8 g.) which, after selenium treatment, yielded the same picrate, m. p. 183—185° (10 mg.), and related solid, m. p. 125—128°, as were obtained in the preceding experiment, and (*b*) a yellow solid, b. p. 200° (0·1 g.), which crystallised from benzene in pale yellow leaflets, m. p. 236—237°, strongly depressed by admixture with the trimethylanthracene described in the previous paragraph. This product also had the ultra-violet absorption of an anthracene derivative; it gave a *s*-trinitrobenzene complex, m. p. 162—164°, and a 2 : 4 : 7-trinitrofluorenone complex, m. p. 183—185°. The amounts were insufficient for analysis.

Ultra-violet Absorption of Polymethylnaphthalenes.—The spectra of the new polymethylnaphthalenes, measured in ethanol, had characteristic naphthalene bands with the strong shift towards the region of longer wave-length which would be expected with such heavy substitution. The Table gives the wave-lengths (in mμ) and extinction coefficients (as logarithms) of the maxima and minima of the two main bands.

	Maxima				Minima	
	(A)		(B)			
Polymethyl derivative	λ	log ε	λ	log ε	λ	log ε
1 : 2 : 3 : 4 : 6-Penta	236	4·87	288	3·69	254	3·20
1 : 2 : 3 : 4 : 5 : 6-Hexa	244	4·86	298	3·87	260	3·19
1 : 2 : 3 : 4 : 5 : 7-Hexa	238	4·82	298	3·85	257	3·14
1 : 2 : 3 : 4 : 6 : 7-Hexa	236	5·13	294	3·73	256	3·24
Hepta	242	4·74	302	3·70	263	3·30
Octa	254	4·70	308	3·70	274	3·31

Maleic Anhydride Addition Compounds of Polymethylnaphthalenes.—The hydrocarbon (0·2 g.) and freshly distilled maleic anhydride (3 g.; *ca.* 30 mols.) in pure dry benzene (4 c.c.) were heated under reflux for 48 hours (somewhat lower yields were obtained after 72 hours). The benzene was removed under reduced pressure and the residue shaken with water until the excess of maleic anhydride had dissolved. The adduct and unchanged hydrocarbon were extracted with ether, and the ether was removed. The residual mixture was boiled for 5 minutes with 5% potassium hydroxide and the unchanged hydrocarbon extracted with ether, the amount being determined after evaporation of the extract. The aqueous solution was acidified and the precipitated acid collected and combined with a further quantity obtained by extraction of the mother-liquor with ether. By dissolving the acid in ethyl acetate containing a few drops of acetic anhydride it was reconverted into anhydride. The Table gives the characteristics of the products.

Polymethyl derivative	Solvent and cryst. form	M. p. of anhydride	Formula	Found (%): C	Found (%): H	Reqd. (%): C	Reqd. (%): H
1 : 2 : 3 : 4 : 6-Penta	Acetone (powder)	138—139°	$C_{19}H_{20}O_3$	76·3	7·3	77·0	6·8
1 : 2 : 3 : 4 : 5 : 6-Hexa	Ethyl acetate (prisms)	134—136	$C_{20}H_{22}O_3$	77·15	7·35	77·4	7·15
1 : 2 : 3 : 4 : 6 : 7-Hexa	Ethyl acetate (cubes)	170 (decomp.)	$C_{20}H_{22}O_3$	77·25	7·25	77·4	7·15
1 : 2 : 3 : 4 : 5 : 6 : 7-Hepta	Ethyl acetate (prisms)	160 (decomp.)	$C_{21}H_{24}O_3$	77·65	7·6	77·7	7·45
Octa	Light petroleum (prisms)	176—178 (decomp.)	$C_{22}H_{26}O_3$	77·8	7·8	78·05	7·7

Oxidation of 1 : 4-*Dihydro*-1 : 2 : 3 : 4 : 5 : 6-*hexamethylnaphthalene*-1 : 4-endo-αβ-*succinic Acid.*—Excess of an 8% solution of potassium permanganate was added slowly to a solution of the anhydride (VI) (0·3 g.) in water (20 c.c.) and sodium hydroxide (2 g.). The mixture was stirred and heated on the steam-bath for 16 hours. Methanol (5 c.c.) was added and the mixture warmed until the solution was decolorised. The filtered solution was concentrated, acidified, and extracted with ether. Evaporation of the extract gave a solid which after crystallisation from water was identified as prehnitic acid, m. p. 235—237° alone or mixed with a specimen prepared by oxidation of prehnitene (lit., 238°).

Oxidation of 1 : 4-*Dihydro*-1 : 2 : 3 : 4 : 6 : 7-*hexamethylnaphthalene*-1 : 4-endo-αβ-*succinic Acid.*—This was carried out as in the previous case, and gave pyromellitic acid, m. p. 271—273°, not depressed with a sample prepared by oxidation of durene (lit., 275°).

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3. *The Crystal and Molecular Structure of Octamethylnaphthalene: A Non-planar Naphthalene Derivative.*

By D. M. DONALDSON and J. MONTEATH ROBERTSON.

Crystals of octamethylnaphthalene have been examined by quantitative *X*-ray analysis. They are orthorhombic, space-group D_{2h}^{22}–*Ccca*, with four molecules of $C_{18}H_{24}$ per unit cell. The molecular symmetry is 222, the asymmetric crystal unit consisting of one-quarter of the chemical molecule. In electron-density projections obtained from two-dimensional Fourier syntheses not all the atoms can be resolved, but the molecule is definitely non-planar. The α-methyl groups are displaced from the mean plane by about 0·73 Å, and the β-methyl groups are displaced in an opposite direction by some smaller amount, probably between 0·25 and 0·40 Å. Symmetry requires an alternate up-and-down displacement of all the methyl groups around the molecule. It is also probable that the naphthalene nucleus itself is distorted, to a smaller extent but in a similar way, but this cannot be definitely established from the data.

INTERESTING stereochemical problems arise in the case of fully substituted naphthalene derivatives, and the synthesis of octamethylnaphthalene by Abadir, Cook, and Gibson (see preceding paper) has now made it possible to study the molecular geometry of this derivative by *X*-ray analysis. Hexamethylbenzene (Lonsdale, *Proc. Roy. Soc.*, 1929, *A*, **123**, 494; Brockway and Robertson, *J.*, 1939, 1324) and durene (Robertson, *Proc. Roy. Soc.*, 1933, *A*, **142**, 659) have already been fully studied by this method, and their carbon atoms are found to be strictly coplanar. In naphthalene, however, another situation arises from the overcrowding of substituents in adjacent α-positions. If there is no distortion, the distance between the centres of such groups would be only 2·4 Å, which is well below the limit expected for non-bonded carbon or atoms of similar size.

In the following analysis it is shown that the molecule of octamethylnaphthalene is far from being planar, and the nature of the distortions observed is described later. The unexpectedly high molecular symmetry displayed in the crystal (three mutually perpendicular two-fold axes but no centre or plane) simplifies the analysis and enables fairly definite conclusions to be reached.

Crystal Data.—Octamethylnaphthalene, $C_{18}H_{24}$; *M*, calc. 240·4, found 238·8; m. p. 174°; *d*, calc. 1·109, found 1·102. Orthorhombic, $a = 16{\cdot}66 \pm 0{\cdot}03$, $b = 11{\cdot}31 \pm 0{\cdot}01$, $c = 7{\cdot}64 \pm 0{\cdot}03$ Å. Absent spectra, (*hkl*) when $h + k$ is odd, (0*kl*) when *k* is odd and when *l* is odd, (*h*0*l*) when *h* is odd and when *l* is odd, (*hk*0) when *h* is odd and when *k* is odd. Space group, D_{2h}^{22}–*Ccca*. Four molecules per unit cell. Molecular symmetry, 222 (three mutually perpendicular two-fold axes). Volume of the unit cell = 1440 Å^3. Absorption coefficient for *X*-rays ($\lambda = 1{\cdot}54$ Å) $\mu = 5{\cdot}44$ per cm. Total number of electrons per unit cell = F(000) = 528.

Crystals were generally obtained as clusters of very small needles, with occasional flat plates developed on (001). No other well-defined faces were observed.

Structure Analysis.—The crystal data show that the asymmetric unit must consist of one-quarter of the chemical molecule, or $4\frac{1}{2}$ carbon atoms. Four of these atoms must repeat in the 16 general positions defined by (000; $\frac{1}{2}\frac{1}{2}0$) + xyz; $\bar{x}\bar{y}z$; $\bar{x}$, $\frac{1}{2}-y$, $\frac{1}{2}-z$; x, $\frac{1}{2}+y$, $\frac{1}{2}-z$; $x\bar{y}\bar{z}$; $\bar{x}y\bar{z}$; $\bar{x}$, $\frac{1}{2}+y$, $\frac{1}{2}+z$; x, $\frac{1}{2}-y$, $\frac{1}{2}+z$; while a fifth carbon atom must lie on one of the two-fold axes, with eight-fold multiplicity. The only chemically reasonable position for the intersection of the three mutually perpendicular two-fold axes, which is taken as the origin of co-ordinates, is the middle of the central bond of the naphthalene nucleus (see I). This point recurs with four-fold multiplicity at 000, $0\frac{1}{2}\frac{1}{2}$, $\frac{1}{2}\frac{1}{2}0$, $\frac{1}{2}0\frac{1}{2}$.

It is clear from (I, that the central bond of the naphthalene nucleus must coincide with one of the two-fold axes, and this molecular direction must therefore be parallel to one

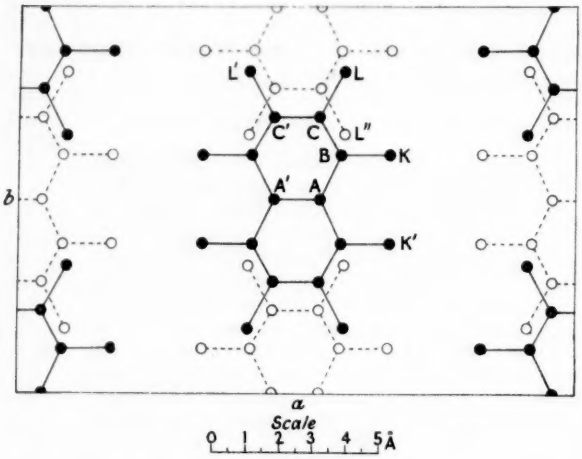
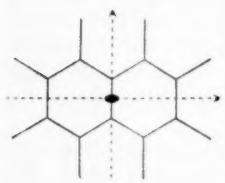


FIG. 1. *Octamethylnaphthalene. Molecular arrangement in projection on* (001).

of the crystal axes, a, b, or c. Packing considerations eliminate the possibility of its being parallel to c (7·64 Å). The two remaining possibilities are easily tested by the calculation of a few orders of the axial structure factors (h00) and (0k0). The fact that the 200 reflection is very much stronger than the 020 immediately indicates that the molecule probably extends along the b direction, with the central bond parallel to a, and this conclusion can be verified by more detailed calculations. For these, the molecule may be assumed, in projection at least, to have the configuration indicated by (I) and normal dimensions ($C_{ar.}$–$C_{ar.}$ ~1·4 Å, $C_{ar.}$–$C_{al.}$ ~1·5 Å). When the (h00) structure factors were evaluated on this basis, good agreements were obtained for eight orders (to 16,000), and a one-dimensional Fourier synthesis showed the expected distribution of scattering matter. The second possibility, that the central bond is parallel to the b-crystal axis, was also tested, but this failed to provide any explanation of the observed intensities.



(I)

The symmetry of the molecules and their orientation in the crystal are now known, but there remains the task of finding the precise position of each atom and hence the details of the molecular geometry. This was studied by trial-and-error methods, the results being refined by means of successive double Fourier syntheses, and difference syntheses, giving projections of the structure along the three axial directions.

The projection along the c axis on (001) provides the most detailed information, but even here many of the atoms are obscured by overlap from molecules lying at different levels in the unit cell. The arrangement required on account of the symmetry and the intensity considerations mentioned above is shown in Fig. 1, where the open circles and dotted bonds

represent molecules situated half a translation along the c axis (perpendicular to the paper) with respect to the standard molecules in the corners and centre. The atoms marked A, B, C, K, and L may be chosen as the asymmetric unit, with origin at the centre of the molecule. The other atoms are derived from these by obvious symmetry operations. It may be noted that if the molecule is planar then all the carbon atoms of any one molecule must lie strictly in the (001) plane; if it deviates from the planar form, then the distortions must be of a regular type, conforming to the 222 molecular symmetry.

Any such distortion from a planar form will have very little effect on the (001) projection, and the simple model shown in Fig. 1, with normal bond lengths, was found to give a good account of all the ($hk0$) reflections. Evaluation of the corresponding double Fourier series consisting of 35 terms (see Table 3) gave the electron-density map shown in Fig. 2. The

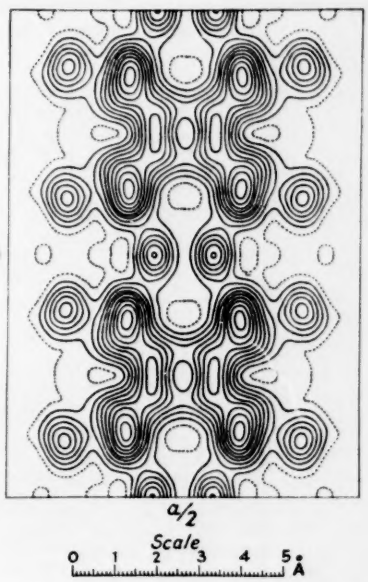


FIG. 2. *Electron-density projection of the octamethylnaphthalene structure on* (001). *Contour lines drawn at intervals of* 1e.Å^{-2}, *the one-electron line being dotted.*

atoms A and K are clearly resolved, but B, C, and L coalesce with symmetry-related peaks to give unresolved doublets. The x and y co-ordinates of all the atoms can, however, be estimated with some accuracy from this projection, and the results are collected in Table 1.

TABLE 1. *Co-ordinates. Origin at intersection of two-fold axes.*

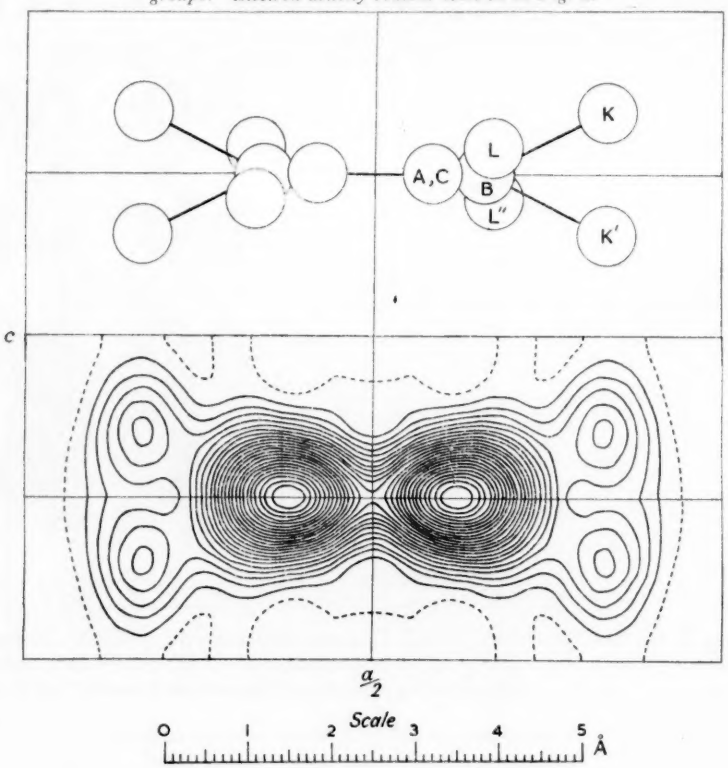
Atom (cf. Fig. 1)	x/a	y/b	z/c	X (Å)	Y (Å)	Z (Å)
A	0·041	0	0	0·690	0	0
B	0·079	0·110	0·034	1·319	1·241	0·259
C	0·042	0·212	−0·012	0·708	2·400	−0·095
K	0·168	0·115	0·095	2·795	1·301	0·726
L	0·086	0·331	−0·034	1·430	3·745	−0·259

The projection of the structure along the b axis on (010) was next considered. A planar model would require the z co-ordinates of all the carbon atoms to be zero, but it was found that the intensities of the ($h0l$) reflections could not be explained on this basis. A consideration of the geometry of the molecule shows that in a planar model the methyl groups K and K' (Fig. 1) attached to the α-positions are over-crowded, the separations being about 2·4 Å, as against 2·9—3·0 Å in hexamethylbenzene and in durene (*locc. cit.*). The most likely distortion therefore consists of a displacement of the group K out of the molecular plane. A trial structure giving the group a displacement of about 0·7 Å from the mean molecular plane led to a reasonable measure of agreement between calculated and observed ($h0l$) reflections, and enabled a double Fourier synthesis to be effected. The resulting

electron distribution is shown in Fig. 3. In this projection the α-methyl groups are quite clearly resolved and the displacement out of the mean plane is very distinct. No other atoms are resolved but the distribution found is hardly compatible with a strictly coplanar arrangement of these other atoms, and corresponds rather to the displaced arrangement shown in the explanatory diagram (upper part of Fig. 3).

Measurement of the projection (Fig. 3) shows that the α-methyl group is displaced by 0·73 Å out of the mean plane. If the z co-ordinates of all the other atoms are given zero values, the average discrepancy between calculated and observed values of the ($h0l$)

FIG. 3. *Octamethylnaphthalene structure projected on* (010), *showing displacement of the* α-*methyl groups. Electron-density contour scale as in Fig. 2.*



structure factors is about 21%. If, however, the β-methyl group (atom L) is given an opposite displacement of about 0·38 Å, as shown in the upper part of Fig. 3, then the average discrepancy in the structure factor calculations falls to about 12%. This displacement may therefore be taken as definite, although its precise amount is uncertain.

Further calculation revealed another possibility, which led to equally good structure factor agreements and provided a more reasonable account of the bond lengths within the molecule, as calculated from the assigned co-ordinates. This was that the atoms in the naphthalene nucleus itself, as well as the methyl groups, may be displaced from a strictly coplanar arrangement. From the symmetry, atom A (Fig. 1) must remain in the (001) plane. If atom B is now moved out of the plane by about 0·2 Å, in the same sense as K, and atom C by about 0·1 Å, in the same sense as L, and the displacement of L reduced from 0·38 Å to about 0·26 Å, then equally good structure-factor agreements are obtained, and these co-ordinates give much more reasonable bond lengths (Table 2).

Although the displacement of the methyl groups out of the mean molecular plane is

definite, the indicated distortion of the naphthalene nucleus cannot be regarded as fully established. It does not seem possible to obtain further evidence from the existing data, as the third projection, along the *a* axis, does not provide any useful information. A full three-dimensional analysis will be required to establish the positions of all the atoms to within narrower limits. In the meantime we have provisionally adopted the model with distorted nucleus in giving the tables of co-ordinates and dimensions above.

TABLE 2. *Interatomic distances (in* Å) *(see* Fig. 1).

A–A' = 1·38	C–C' = 1·43	$K \ldots K'$ (α-$CH_3 \ldots \alpha$-CH_3) = 2·98
A–B = 1·42	B–K = 1·55	$K \ldots L$ (α-$CH_3 \ldots \beta$-CH_3) = 2·97
B–C = 1·36	C–L = 1·54	$L \ldots L'$ (β-$CH_3 \ldots \beta$-CH_3) = 2·91

Note. Intermolecular distances have not been evaluated in detail, as the z co-ordinates are uncertain. The distance between the mean planes of the molecules whose ends overlie each other (Fig. 1) is $\frac{1}{2}c$ = 3·82 Å.

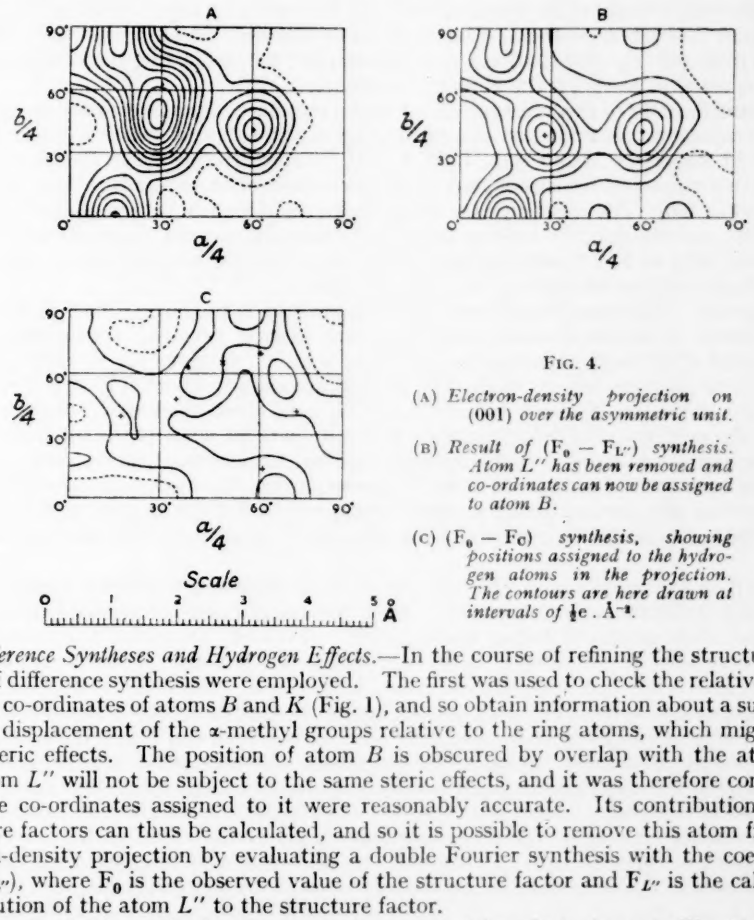


FIG. 4.

(A) *Electron-density projection on* (001) *over the asymmetric unit.*

(B) *Result of* ($F_0 - F_{L''}$) *synthesis. Atom L'' has been removed and co-ordinates can now be assigned to atom B.*

(C) ($F_0 - F_C$) *synthesis, showing positions assigned to the hydrogen atoms in the projection. The contours are here drawn at intervals of* $\frac{1}{2}$e . Å^{-3}.

Difference Syntheses and Hydrogen Effects.—In the course of refining the structure, two types of difference synthesis were employed. The first was used to check the relative values of the y co-ordinates of atoms B and K (Fig. 1), and so obtain information about a suspected mutual displacement of the α-methyl groups relative to the ring atoms, which might arise from steric effects. The position of atom B is obscured by overlap with the atom L''. The atom L'' will not be subject to the same steric effects, and it was therefore considered that the co-ordinates assigned to it were reasonably accurate. Its contribution to the structure factors can thus be calculated, and so it is possible to remove this atom from the electron-density projection by evaluating a double Fourier synthesis with the coefficients (F_0—$F_{L''}$), where F_0 is the observed value of the structure factor and $F_{L''}$ is the calculated contribution of the atom L'' to the structure factor.

The result of this synthesis, taken over the asymmetric unit, is shown in Fig. 4(B), while Fig. 4(A) shows for comparison the original synthesis over the same area. The atom B is now clearly resolved and its co-ordinates can be estimated with some accuracy. The y co-ordinate is found to differ from that originally assigned by 0·06 Å. As it had earlier been given the same y co-ordinate as atom K, there is now evidence that the methyl groups

K and K' are mutually displaced by about 0·06 Å, in the b direction. The correctness of the co-ordinates obtained from this synthesis, of course, depends upon the accuracy of the co-ordinates and scattering curve assigned to the atom L''. These are probably reliable, and it is noteworthy that the (F_0—$F_{L''}$) synthesis reproduces the positions of the previously resolved atoms A and K to within 0·01 Å.

A normal difference synthesis employing the coefficients (F_0—F_C), where F_0 is the measured structure factor and F_C the value calculated from the combined carbon contributions, was also carried out for this zone. The object was to estimate the hydrogen contributions, which must be considerable in this compound, as 18% of the scattering matter consists of hydrogen electrons. The result of this synthesis is shown in Fig. 4(c), where some well-defined ridges at the 1—1·5 electron level in the neighbourhood of the methyl groups probably indicate the average hydrogen positions. For purposes of calculation, the six hydrogen atoms which must be associated with the asymmetric unit have been assigned mean positions which are indicated by the small crosses in Fig. 4(c). These are compatible with a tetrahedral distribution about the methyl groups, at distances of about 1·08 Å from the carbon centres. Apart from these features, the electron-density diagram obtained from the (F_0—F_C) synthesis is comparatively flat, indicating that no large errors have been made in assigning the atomic co-ordinates.

The contributions of the hydrogen atoms to the structure factors were now calculated in a manner similar to that adopted in investigating the structure of hexamethylenediamine (Binnie and Robertson, *Acta Cryst.*, 1950, **3**, 424). The scattering curve used is of similar shape to that employed for carbon, but of one-sixth the height, and falls rapidly to zero at about $\sin\theta = 0{\cdot}6$. The effect of these additions to the structure factors of the ($hk0$) zone is, however, considerable, the average discrepancy between calculated and observed values falling from 20% to 14·7% with the inclusion of the hydrogen contributions. The results of the structure-factor calculations are given in Table 3.

Discussion.—The most striking result of this analysis is the large extent to which the carbon atoms of octamethylnaphthalene deviate from a coplanar arrangement. The displacement of the methyl groups attached to the α-carbon atoms can be measured directly on one of the electron-density maps (Fig. 3), and amounts to about 0·73 Å. This corresponds to a deviation of about 28° of the C–CH_3 bond from the mean molecular plane. There is also evidence that these bonds are not quite parallel, when projected on the mean molecular plane, but show a slight outwards mutual displacement, amounting to about 0·06 Å for each methyl group. It is highly probable that the methyl groups attached to the β-positions also deviate from the planar arrangement, but the amount of the displacement in this case cannot be estimated with certainty. It probably lies between 0·25 and 0·40 Å.

There is an ambiguity concerning the sense of these displacements, which arises from the form of the structure-factor expressions, when the calculations are confined to the two-dimensional data employed in this investigation. However, a study of the model shows that the only feasible movements for the adjacent α- and β-methyl groups are in opposite sense, one above and one below the mean molecular plane. When this is decided for any two groups, say K and L (Fig. 1), then the crystal symmetry demands that all the eight methyl groups should likewise be displaced alternately above and below the mean plane. It is noteworthy that these displacements now give a clearance between adjoining methyl groups around the naphthalene nucleus which is almost exactly equal to that found in durene and in hexamethylbenzene (*locc. cit.*). The separations are given in Table 2.

The evidence concerning corresponding movements of the atoms in the naphthalene nucleus itself is very indirect. It can only be said that such displacements, of about 0·1—0·2 Å and in the same sense as the displacements of the methyl groups, are compatible with the X-ray evidence, but are not as yet conclusively proved by that evidence. It is known that in naphthalene itself the atoms are very rigidly coplanar (see, *e.g.*, Coulson, Daudel, and Robertson, *Proc. Roy. Soc.*, 1951, *A*, **207**, 306). However, when the bonds to the methyl groups are forced out of the naphthalene plane, the state of regular trigonal hybridization around each carbon atom will be destroyed. If an attempt is made to maintain a coplanar arrangement for the three bonds emanating from each ring-carbon atom,

and at the same time to displace the methyl groups in the way that has been observed, then it is necessary to displace the ring-carbon atoms from the mutually coplanar arrangement in just the way that is suggested by the *X*-ray data. In this way the regular trigonal symmetry of the bonds about each ring atom can be retained, but the bonds between

TABLE 3. *Measured and calculated values of the structure factor.*

(Hydrogen contributions are included in the (*hk*0) zone for planes with 2 sin θ <1·20.)

hkl	2 sin θ (λ = 1·542)	F, meas.	F, calc.	*hkl*	2 sin θ (λ = 1·542)	F, meas.	F, calc.	*hkl*	2 sin θ (λ = 1·542)	F, meas.	F, calc.
200	0·185	170	162	14,6,0	1·530	<7	−2	804	1·094	17	−22
400	0·370	70	−67	16,6,0	1·690	<6	−5	10,0,4	1·226	<10	−6
600	0·555	43	−47	18,6,0	1·854	7	−4	12,0,4	1·371	10	−12
800	0·739	100	−109	280	1·106	12	−1	14,0,4	1·524	<8	−1
10,0,0	0·924	23	−24	480	1·150	<7	−2	16,0,4	1·684	<9	−7
12,0,0	1·109	22	−28	680	1·222	<7	13	18,0,4	1·848	<7	−9
14,0,0	1·294	14	−12	880	1·316	14	−11	206	1·224	24	33
16,0,0	1·479	11	−20	10,8,0	1·428	11	−8	406	1·265	14	13
18,0,0	1·664	<6	−7	12,8,0	1·554	<7	8	606	1·332	<10	−21
20,0,0	1·849	<5	−4	14,8,0	1·691	<6	−2	806	1·418	<10	−6
020	0·272	59	−57	16,8,0	1·837	<5	−1	10,0,6	1·522	<10	−5
040	0·545	82	−90	18,8,0	1·989	<1	1	12,0,6	1·641	<9	−14
060	0·817	21	20	2,10,0	1·374	9	14	14,0,6	1·772	<7	−2
080	1·089	23	26	4,10,0	1·411	<7	2	16,0,6	1·910	<5	−2
0,10,0	1·362	19	32	6,10,0	1·471	<7	2	208	1·624	<9	8
0,12,0	1·634	<7	−5	8,10,0	1·550	<7	−13	408	1·654	<9	6
0,14,0	1·906	<4	−4	10,10,0	1·646	<7	−11	608	1·705	<8	2
220	0·329	48	−43	12,10,0	1·756	<6	−1	808	1·774	<7	1
420	0·459	5	7	14,10,0	1·879	<4	−4	10,0,8	1·859	<6	−6
620	0·618	11	24	2,12,0	1·644	<7	2				
820	0·787	7	5	4,12,0	1·675	<6	−2	022	0·486	39	−41
10,2,0	0·963	<6	2	6,12,0	1·726	<6	−8	042	0·678	26	−25
12,2,0	1·142	<6	3	8,12,0	1·793	<5	3	062	0·911	9	19
14,2,0	1·322	<7	3	10,12,0	1·877	<5	6	082	1·161	17	11
16,2,0	1·504	<7	4	12,12,0	1·975	<2	1	0,10,2	1·420	19	22
18,2,0	1·686	<6	3					0,12,2	1·683	<10	−2
20,2,0	1·869	<5	−2	002	0·403	291	266	0,14,2	1·948	<5	−1
240	0·576	30	35	004	0·806	76	73	024	0·851	14	−22
440	0·659	69	76	006	1·210	20	18	044	0·973	25	23
640	0·778	34	23	008	1·613	<9	9	064	1·148	<11	18
840	0·918	26	23	202	0·444	156	137	084	1·355	<12	−5
10,4,0	1·073	22	−25	402	0·547	11	−18	0,10,4	1·583	12	8
12,4,0	1·236	50	−56	602	0·686	65	−66	0,12,4	1·822	<9	2
14,4,0	1·404	14	−15	802	0·842	61	−65	026	1·240	<11	−8
16,4,0	1·576	<7	2	10,0,2	1·008	16	−16	046	1·327	16	21
18,4,0	1·751	<6	2	12,0,2	1·180	<9	11	066	1·460	<12	10
20,4,0	1·928	7	7	14,0,2	1·355	<10	−7	086	1·628	<11	−4
260	0·838	19	21	16,0,2	1·532	<10	−15	0,10,6	1·822	<9	3
460	0·897	5	−6	18,0,2	1·711	<8	−9	028	1·636	<11	−1
660	0·988	16	−18	20,0,2	1·891	<6	−2	048	1·703	<10	7
860	1·102	<6	2	204	0·827	78	80	068	1·808	<9	1
10,6,0	1·233	13	6	404	0·887	16	13	088	1·946	<5	1
12,6,0	1·377	14	−3	604	0·979	42	−53				

adjoining ring atoms become twisted. These relations become evident when one examines a rigid molecular model and tries to impose on it the required distortions.

Some interesting stereochemical possibilities are suggested by these results, which we hope to examine in other simple naphthalene derivatives and related compounds.

EXPERIMENTAL

Copper-K_α radiation, λ = 1·542 Å, was employed in all the measurements. Rotation, oscillation, and moving-film photographs were taken from crystals rotated about all the principal zone axes, and these were analysed in the usual way to determine the cell dimensions and systematic halvings, from which the space-group could be determined uniquely.

The density was accurately determined, in order to check the molecular weight of the compound, by flotation in sodium chloride solution, with evacuation and use of detergent to ensure freedom from trapped air. With four crystals (all very small) the values obtained were 1·098, 1·109, 1·108, 1·092, mean 1·102. Four molecules being assumed in the unit cell, the

corresponding molecular weights are 238·0, 240·4, 240·2, 236·7, mean 238·8 [Calc. for $C_{18}H_{24}$: 240·4. Calc. for $C_{17}H_{22}$ (heptamethylnaphthalene), 226·3].

For the intensity measurements, small crystals were employed, with cross-sections normal to the rotation axes of 0·12 × 0·35 mm. for the (*hk*0) zone, and 0·42 × 0·46 mm. for the (*h*0*l*) zone. The crystals were completely bathed in a uniform *X*-ray beam. The absorption coefficient is low (μ = 5·44 per cm.) and no corrections were applied. The multiple-film technique (Robertson, *J. Sci. Instr.*, 1943, **20**, 175) with visual estimation was employed, the total range of intensities covered being about 7500 to 1.

The usual formulæ for mosaic-type crystals being used, the structure factors were evaluated and are listed in Table 3 under " F, meas.". The absolute scale was obtained at a later stage by correlation with the final calculated values. In deriving the calculated values from the coordinates in Table 1, the empirical atomic scattering curve derived from the naphthalene analysis (Abrahams, Robertson, and White, *Acta Cryst.*, 1949, **2**, 233) was used. The discrepancies between the calculated and observed structure factors, expressed as a percentage of the total measured structure factors, amounts 14·2% for all planes from which reflections were recorded.

The Fourier syntheses were calculated by the usual formulæ, and by means of the three-figure strip and stencil method (Robertson, *J. Sci. Instr.*, 1948, **25**, 28). The asymmetric unit is of small area, and the axial sub-divisions employed for the calculations were $a/120$ = 0·139 Å, $b/60$ = 0·189 Å, $c/60$ = 0·127 Å.

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4. *Kestose: a Trisaccharide formed from Sucrose by Yeast Invertase.*

By N. ALBON, D. J. BELL, P. H. BLANCHARD, D. GROSS, and J. T. RUNDELL.

The trisaccharide kestose, one of the oligosaccharides synthesised during the action of yeast invertase preparations on concentrated sucrose solutions, has been isolated by chromatography on a cellulose column. It is composed of two radicals of D-fructose and one of D-glucose; some of its properties have been determined. Analysis of the cleavage products of the methylated sugar show that it is *O*-α-D-glucopyranosyl(1→2)*O*-β-D-fructofuranosyl(6→2)β-D-fructofuranoside.

As a result of specificity (cf. Levi and Purves, *Adv. Carbohydrate Chem.*, 1949, **4**, 1; Gottschalk, *ibid.*, 1950, **5**, 49) the invertase of yeast is considered to be a β-fructofuranosidase, *i.e.*, it specifically attacks the fructofuranoside linkage in the sucrose molecule. The progress of sucrose hydrolysis has usually been followed polarimetrically in the assumption that equal parts of glucose and fructose are formed. However, Bacon and Edelman (*Arch. Biochem.*, 1950, **28**, 467) and Blanchard and Albon (*ibid.*, 1950, **29**, 220) showed that incomplete hydrolysis of sucrose by a variety of yeast invertase preparations produced, in addition to fructose and glucose, a number of higher oligosaccharides which were themselves eventually broken down to fructose and glucose. These results were confirmed by Fischer, Kohtès, and Fellig (*Helv. Chim. Acta*, 1951, **34**, 1132) using a highly purified yeast enzyme preparation. White and Secor (*Arch. Biochem. Biophys.*, 1952, **36**, 490) have determined the ratios of fructose to glucose in a number of these oligosaccharides. Several authors have suggested that invertases should be regarded as fructose radical-transferring enzymes, and Bacon (*Biochem. J.*, 1952, **50**, xviii) has demonstrated that a yeast invertase preparation can transfer these radicals from sucrose to various alcohols to form fructosides. Barton-Wright and Harris (*Nature*, 1951, **167**, 560) have shown that oligosaccharide excretion takes place when yeasts are grown on a sucrose medium.

A similar fructose-transferring effect has also been observed during the action of mould preparations on sucrose (Bealing and Bacon, *Biochem. J.*, 1951, **49**, lxxv; Pazur, *Fed. Proc.*, 1952, **11**, 267). Again the oligosaccharides were themselves eventually completely hydrolysed. Bealing and Bacon (*Biochem. J.*, 1952, in the press) have concluded that the

mould invertase responsible for this effect is a β-fructofuranosidase similar to, but not identical with, that of yeast invertase.

Preliminary work showed that oligosaccharides were produced in a yield of at least 6% (calculated on the original sucrose) when yeast invertase acted on concentrated sucrose solutions, the greatest amount being present when about 50% of the sucrose had been consumed ("50% hydrolysis"). When no sucrose remained, no oligosaccharides were detectable. The method of preparation of the enzyme did not appear to matter; a number of different yeast preparations gave identical results.

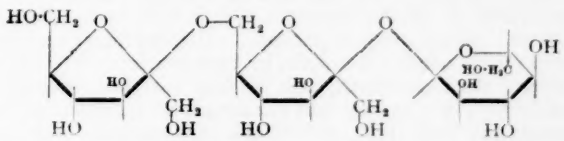
In the present preparative work, a 50% (w/w) sucrose solution was "50% hydrolysed" by a commercial yeast invertase preparation at pH 4·5 and the product analysed by paper-chromatography (de Whalley, Albon, and Gross, *Analyst*, 1951, **76**, 287; Albon and Gross, *ibid.*, 1952, **77**, 406, 410). This led to three oligosaccharide spots in addition to those of sucrose, fructose, and glucose. Using Bacon and Edelman's nomenclature (*loc. cit.*) we have termed these spots components III, II, and I; their respective R_F^{22} values were 0·12, 0·14, and 0·19, that of sucrose being 0·24. The product from 60 g. of sucrose was then separated on a large column of powdered cellulose (Hough, Jones, and Wadman, *Nature*, 1948, **162**, 448; *J.*, 1949, 2511) as modified for large-scale separation by Gross and Albon (*Analyst*, 1952, in the press). Component III was obtained from a number of fractions. Crystallised from methanol it was chromatographically at least 95% pure and gave a positive Raybin reaction (Raybin, *J. Amer. Chem. Soc.*, 1933, **55**, 2603; 1937, **59**, 1402). Hydrolysis to completion by yeast invertase produced two parts of fructose and one of glucose, but paper chromatograms at intermediate stages revealed spots in the position expected for sucrose. A molecular-weight determination confirmed the trisaccharide structure.

A report on the industrial significance of this sugar, to which the name kestose has been assigned, has already appeared (de Whalley, *Int. Sugar J.*, 1952, **54**, 127).

Kestose was methylated in the usual way, in good yield, to an undecamethyl ether, which was hydrolysed by 0·04N-sulphuric acid to 1 : 3 : 4 : 6-tetramethyl fructose, 2 : 3 : 4 : 6-tetramethyl glucose, and 1 : 3 : 4-trimethyl fructose (detected chromatographically on paper). The rotation of the hydrolysate indicated that the three components were present in equimolecular amounts. Quantitative chromatography (Bell and Palmer, *J.*, 1949, 2522) separated the trimethyl component as pure crystalline 1 : 3 : 4-trimethyl-D-fructose, and, judged from its specific rotation, the residue was an equimolar mixture of the tetramethyl components.

An attempt was made to separate the tetramethyl sugars (280 mg. in all) by Haworth and Mitchell's procedure (*J.*, 1923, **123**, 308). Control experiments showed that the 1 : 3 : 4 : 6-tetramethyl methylfructofuranoside formed was so volatile as largely to escape condensation even at low temperatures and moderately reduced pressures. The tetramethyl glucopyranose was, however, recovered crystalline. The methylated kestose products yielded crystalline 2 : 3 : 4 : 6-tetramethyl D-glucopyranose, but the ketoside recovered was insufficient for certain identification. The polarimetric behaviour of the mixed sugars in dry methanol containing 0·25% of hydrogen chloride was, however, fully consistent with that of equimolar proportions of the two sugars named above.

We therefore consider that kestose originates in the catalytic addition to sucrose of a fructofuranose radical transferred from a second sucrose molecule (cf. White, *Arch.*



(I)

Biochem. Biophys., 1952, **39**, 238). From the known specificity of yeast invertase, the newly formed fructoside link must be presumed to be of the β-type. Kestose would therefore be *O*-α-D-glucopyranosyl(1→2)*O*-β-D-fructofuranosyl(6→2)β-D-fructofuranoside (I)

A similar trisaccharide ($[\alpha]_D^{20}$ +23°) has been isolated by Dedonder (*Compt. rend.*,

1951, **232**, 1134; *Bull. Soc. Chim. biol.*, 1952, **34**, 144) from an extract of tubers of the Jerusalem artichoke, and termed by him "Glucofructosane B." It seems probable (cf. also Bacon and Edelman, *Biochem. J.*, 1951, **48**, 114) that the carbohydrates of such tubers form a series structurally related to inulin, and it might be expected that the trisaccharide found by Dedonder would possess the typical 2 : 1′-link between the fructose radicals. However, Pazur (personal communication) has isolated from the products of the action of a mould extract on sucrose a trisaccharide ($[\alpha]_D$ +17°) to which he ascribes the 2 : 1′-linkage. This may be identical with component II produced by the yeast invertase reaction, which is present in rather smaller amount than is kestose.

Experimental

Evaporations were conducted below 45° with adequate pH control. Rotations were determined in 2-dm. tubes. Elementary analyses were by Drs. Weiler and Strauss, Oxford.

Paper-chromatographic Examination of Partly Inverted Sucrose.—The solvent was *n*-propanol–ethyl acetate–water (7 : 2 : 1, by vol.). Chromatograms were run for 48 hours at 22° and sprayed (for ketoses) with a 10 : 1 mixture of 2% alcoholic α-naphthol and phosphoric acid. For R_F values see p. 25.

Large-scale Fractionation of Partly Inverted Sucrose.—A solution of sucrose (60 g.) in water (54 ml.) was adjusted to pH 4·5 with acetic acid. "Sumasuco" Invertase Concentrate (Sugar Manufacturers Supply Co.) (6 ml.) was added and the solution kept at 20° for 40 minutes (approx. time for 50% inversion). The reaction was then stopped by boiling for a few seconds. A glass tube of 5-in. diameter was packed to a depth of 12·5 in. with ashless cellulose powder (Whatman standard grade) (*ca.* 1·7 kg.), and the column washed with de-aerated water followed by the eluting solvent (*iso*propanol–butanol–water, 7 : 1 : 2 by vol.). The partly inverted sucrose, dissolved in this solvent (800 ml.), was placed on the column, allowed to soak in, and eluted at the rate of 100 ml. per hour. Fractions of 80 ml. (14 l. in all) were collected by means of an automatic drop-counting fraction-collector. Elution of the sugars was followed by paper chromatography. The fractions from 9—12 l. of the eluate contained chromatographically pure kestose (component III).

Isolation of Kestose.—The fractions containing kestose alone were evaporated, taken up in methanol (70 ml.), and again evaporated to remove water and butanol. A solution of the residue in methanol (140 ml.) was filtered, concentrated to 20 ml., and kept in a desiccator (silica gel) at room temperature; the *kestose* (1·75 g.) which then crystallised was washed with methanol and dried to constant weight *in vacuo* at 50°, showing no loss in weight at 105°. It had m. p. 145° ± 2° (uncorr.), $[\alpha]_D^{20}$ +27·3° (*c*, 2·19 in H_2O) (Found: C, 42·3; H, 6·5. $C_{18}H_{32}O_{16}$ requires C, 42·9; H, 6·4%). The molecular weight (489; error ±4%) ($C_{18}H_{32}O_{16}$ requires 504) was determined by an unpublished cryoscopic semimicro-method due to Gross, a thermistor resistance thermometer (Standard Telephones and Cables Ltd.) being used after calibration against a Beckmann thermometer.

The sugar was very soluble in water and was not sweet. It crystallised from methanol and (with some difficulty) from water as fragile rhomboidal plates. It was non-reducing to Fehling's solution and ammoniacal silver nitrate under mild conditions. It gave a positive Raybin reaction. After complete hydrolysis by yeast invertase the specific rotation of the reaction mixture agreed with a mixture of two parts of fructose and one of glucose. This was confirmed by chromatographic comparison, and by estimating (*a*) total reducing power (Somogyi, *J. Biol. Chem.*, 1937, **117**, 771) and (*b*) ketose, as fructose (Roe, *J. Biol. Chem.*, 1934, **107**, 15).

Methylation.—All organic solvents used were distilled from glass apparatus. To kestose (1 g.), in dioxan (10 ml.) and 30% (w/v) sodium hydroxide solution (10 ml.), rapidly stirred at room temperature, were added, at 10-min. intervals, 30% sodium hydroxide solution (80 ml.) and methyl sulphate (40 ml.), each in 10 equal portions. After 0·5 hour's heating of the stirred reaction mixture at ~100°, the product was isolated by three partitions into chloroform. After evaporation of the solvent, the crude methylated kestose was thrice treated with Purdie's reagents, the final product (0·77 g.; average loss per treatment ~10%) being isolated from a ethereal solution (charcoal) and dried (P_2O_5–NaOH) in a high vacuum. The resulting *undecamethyl kestose* was a non-reducing syrup, $[\alpha]_D^{18}$ +25·8° (*c*, 4·2 in H_2O), +20·1° (*c*, 3·5 in $CHCl_3$), n_D^{20} 1·4060 (difference per 1°, ±0·00036) (Found: C, 52·0; H, 8·3; OMe, 51·8. $C_{29}H_{54}O_{16}$ requires C, 52·3; H, 8·2; OMe, 51·8%).

Hydrolysis of Methylated Kestose and Paper Chromatography of the Hydrolysate.—The ether (0·693 g.) in 0·04N-sulphuric acid (25 ml.) was heated at ~100° until a constant optical rotation

was observed (60 min.; $[\alpha]_D^{20}$ +19° *c*, 4). A specimen of the evaporated solution, neutralised by barium carbonate and filtered, was examined by paper chromatography. A single aldose, corresponding to 2 : 3 : 4 : 6-tetramethyl glucose, and two ketoses corresponding to 1 : 3 : 4 : 6-tetramethyl fructose and 1 : 3 : 4-trimethyl fructose were the sole components of the mixture. These three sugars (in the D-configuration) in equimolar proportions would show $[\alpha]_D^{20}$ +18·7° (in H_2O), a figure calculated from the following respective values found at 20·0° for chromatographically pure materials: +81·5° (West and Holden, *Org. Synth.*, 1940, **20**, 97; Greville and Northcote, *J.*, 1952, 1945); −55·7° (Bell, unpublished); +30·3° (Bell, unpublished). Tetramethyl derivatives of D-glucofuranose and of D-fructopyranose could not have been present in detectable amounts. Aniline phthalate and resorcinol–hydrochloric acid sprays were used to detect aldoses and ketoses respectively (cf. Bell and Palmer, *loc. cit.*).

Identification of the Cleavage Products of Methylated Kestose.—15 Ml. of the above hydrolysate were evaporated and the resulting syrup was chromatographed (Bell and Palmer, *loc. cit.*) on a 15-g. silica–water column, the mobile phase being 30 column-lengths of toluene–0·33% ethanol. Evaporation of the eluate yielded tetramethyl hexoses (280 mg.), $[\alpha]_D^{20}$ 55·0° in H_2O, corresponding to an equimolar mixture of 2 : 3 : 4 : 6-tetramethyl D-glucose and 1 : 3 : 4 : 6-tetramethyl D-fructose. Paper chromatograms showed two spots only, which corresponded exactly to these two substances. The aqueous solution of this mixture, which had been used to determine the specific rotation, was evaporated by freeze-drying; even then some of the fructose component volatilised (Bell and Palmer, *loc. cit.*). The dried material was dissolved in dry methanol (25 ml.) containing 0·25% of hydrogen chloride (w/w) and the polarimetric behaviour observed in a 4-dm. tube at 18°. The initial $[\alpha]_D$ (+52·5°) (calc. from approx. wt. of sugars) rose to a constant value of +70° in 24 hours. This behaviour is expected from an equimolar mixture of the suspected two sugars (cf. Haworth and Mitchell, *loc. cit.*). After isolation in the usual way, the reaction product was heated at 70°/0·1 mm. under a condenser cooled by acetone–solid carbon dioxide. The non-volatile residue crystallised; after trituration with a little light petroleum (b. p. 40—60°) the crystals melted at 94—96° alone or mixed with authentic 2 : 3 : 4 : 6-tetramethyl D-glucose. The amount of the distillate was too small to permit more than paper chromatographic examination, after appropriate hydrolysis; a single spot identical with 1 : 3 : 4 : 6-tetramethyl fructose was obtained. A control experiment with the same amount of an equimolar mixture of the two tetramethyl sugars gave similar results.

A methanolic extract of the stationary phase of the silica column yielded a colourless syrup (130 mg., *ca.* 100%) which rapidly crystallised. Paper chromatography indicated that 1 : 3 : 4-trimethyl fructose was the sole component. The material, without further recrystallisation, had n_D^{20} 1·4658, m. p. 68—71° alone or mixed with 1 : 3 : 4-trimethyl D-fructose (m. p. 70—73°), $[\alpha]_D^{19}$ −55·0° (*c*, 2·5 in H_2O; equil.). Chromatographically pure 1 : 3 : 4-trimethyl D-fructose, examined under identical conditions, had $[\alpha]_D^{19}$ −55·2°.

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5. *Some Physical Properties of Uranium Hexafluoride.*

By D. R. Llewellyn.

A number of physical constants of uranium hexafluoride are determined. The density of the liquid was measured between 65° and 100° and that of the vapour from 0° to 100°. The specific heat was determined from −60° to +100° and the data were used, together with the vapour-pressure measurements from −15° to +100°, to calculate a vapour-pressure equation for solid and liquid. The critical temperature, melting point, and heat of melting are recorded. The viscosity, surface tension, and refractive index of the liquid were measured between 65° and 100°. The thermal conductivity of the vapour was measured at 5° and 105°, and the viscosity over a temperature range 0—200°. The heat of vaporization of solid and liquid, Sutherland's constant, the mean free path, the parachor, and the molecular refraction have been calculated.

Uranium hexafluoride was first prepared by Ruff (*Ber.*, 1909, **42**, 495) who described it as a pale yellow, hygroscopic, very reactive substance, and a strong fluorinating agent. A preliminary investigation of its chemical properties confirmed its fluorinating ability but showed that, by following the precautions and techniques now described, the pure substance could be handled satisfactorily in glass apparatus.

Uranium hexafluoride is rapidly hydrolysed by water with the formation of uranyl fluoride and hydrogen fluoride (cf. Amphlett, Mullinger, and Thomas, *Trans. Faraday Soc.*, 1948, **44**, 927). This was very troublesome because glass, in the presence of only minute traces of water or hydrogen fluoride, was severely etched by the hexafluoride, probably owing to the reactions $UF_6 + 2H_2O \longrightarrow UO_2F_2 + 4HF$ and $SiO_2 + 4HF \longrightarrow SiF_4 + 2H_2O$. Either of these reactions can initiate the chain.

Ruff states erroneously that the hexafluoride combines vigorously with potassium or sodium fluoride. Presumably his salts were imperfectly dried, because experiments have shown that uranium hexafluoride can remain in contact with these salts for long periods with only an initial colour change from white to very pale yellow. Addition of potassium fluoride to a UF_6–HF mixture in glass apparatus breaks the decomposition chain reaction.

Special attention was paid to reactivity of the hexafluoride towards metals and its behaviour in the presence of certain organic compounds—particularly waxes and oils used in high-vacuum technique.

Corrosion tests were carried out on a number of metals and alloys. Nickel, copper, and brass were apparently unattacked after long exposure to the vapour at room temperature. At higher temperatures, copper and brass, which would withstand attack at 100° for limited periods, were not as resistant as nickel, which was apparently unattacked after many weeks' exposure under the same conditions. Mercury at room temperature rapidly became coated with a black film.

Uranium hexafluoride was very reactive towards most organic compounds. In general, it was reduced to the tetrafluoride, hydrogen fluoride was evolved, and a carbonaceous mass deposited. The reaction with Apiezon grease " L " was slow, and this grease, when not contaminated with water, was a satisfactory lubricant for taps. Dried and degassed Apiezon oil " A " was only slowly attacked, but the reaction was too rapid to allow the use of this oil in manometers in contact with uranium hexafluoride. Apiezon waxes " W " and " W100 " were not visibly attacked at room temperature and could be used for joining metal to glass, although wherever possible this was accomplished through a copper–glass seal.

The determination of the several physical properties is described below. When this work was started no reliable data on the properties of uranium hexafluoride had been published, but various publications have since recorded certain properties. These are noted, and the results compared with those reported here, chiefly in the discussion of the data (p. 34).

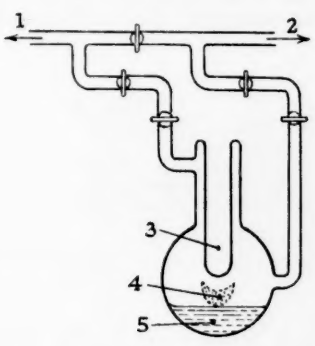
Experimental

The uranium hexafluoride was handled at 10^{-5} mm. The pressure in the main pumping line was indicated continuously by a Pirani gauge, calibrated at frequent intervals against a McLeod gauge (to detect any sudden change in its characteristics occasioned by corrosion of the filament by uranium hexafluoride). Once assembled, the apparatus was kept under a high vacuum whenever possible. Before the introduction of uranium hexafluoride, all accessible parts were heated with a flame and pumping was continued for at least 10 days.

The large coefficient of expansion of uranium hexafluoride between −180° and room temperature would not permit the solid to be condensed at a low temperature on to the concave surface of a normally shaped vessel, but a collecting vessel of the type shown in Fig. 1, with the condensing agent in the re-entrant tube, was satisfactory. The entrance and exit to this storage vessel were controlled by two taps in series. The inner taps were only closed in order to regrease the remainder.

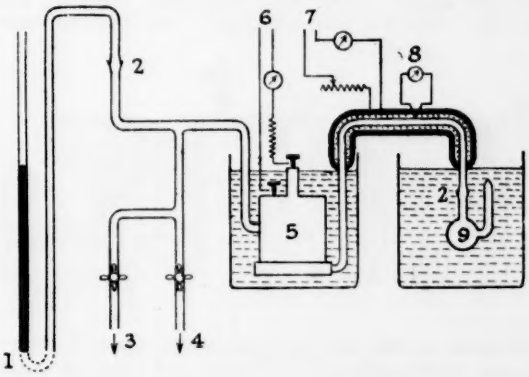
When it was necessary to have a large quantity of the hexafluoride in a vessel of normal shape it was usually convenient to transfer it in the liquid phase. The apparatus to be filled was sealed on to a vessel with a re-entrant tube, and excess of fluoride was distilled into this

Fig. 1.



1, *To pumps.*
2, *To apparatus.*
3, *Condensing agent.*
4, *Uranium hexafluoride.*
5, *Potassium fluoride.*

Fig. 2.



1, *Mercury manometer.*
2, *Copper–glass seals.*
3, *To pumps.*
4, *To compressed air supply.*
5, *Bellows manometer (null instrument).*
6, 2-v *Supply.*
7, 230-v *Supply.*
8, *Thermocouple.*
9, *Glass bulb for uranium hexafluoride.*

vessel which was then sealed off from the main reservoir. The vessel and adjoining apparatus were immersed in a thermostat at 70°, and the molten hexafluoride poured from the vessel to the apparatus, which was then cooled and sealed off.

Uranium hexafluoride was received in glass vessels fitted with mechanical breakers. Hydrogen fluoride, which may have been present, or formed by reaction with water or organic material, was removed by introducing into all reservoirs a quantity of carefully dried and degassed potassium fluoride. The chief impurities were silicon tetrafluoride and freshly liberated hydrogen fluoride, both of which have appreciable vapour pressure at −20°. All samples of hexafluoride were purified by repeated distillation into reservoirs at this temperature, and the purity tested by analysis for uranium content, and by taking the vapour pressure at 0°.

Density.—(i) *Liquid* (70—100°). The density of liquid uranium hexafluoride was determined by sealing a known weight in a calibrated tube, and measuring the volume at various temperatures. A Pyrex tube, 25 cm. long and of 1 mm. internal diameter, was chosen for its uniform bore, and a bulb of 3 cm. diameter blown on one end. The capacity of the bulb and bore of the capillary were determined by distilling into them various amounts of mercury and determining the distance of the meniscus from the base of the bulb at different temperatures for each weight of mercury. The bulb was filled with liquid uranium hexafluoride at 105° as described above, and, after cooling, the top of the capillary was sealed. The position of the meniscus was determined between 70° and 100°. The weight of the hexafluoride was obtained by breaking the capillary and rapidly distilling out the contents. The determination

was repeated with various samples of uranium hexafluoride. The results were as shown below, values at round temperatures being given on p. 36.

Temp.	68·0°	71·6°	74·0°	76·0°	78·2°	81·8°	84·0°	87·8°	91·6°	93·8°	98·6°	98·9°
d, g. cm.$^{-3}$	3·620	3·582	3·581	3·560	3·542	3·525	3·520	3·484	3·455	3·448	3·427	3·416

(ii) *Vapour* (0—100°/0—20 mm.). Two 4-l. flasks were joined and immersed in a thermostat. Gaseous connection was made through narrow-bore leads to a bellows manometer (cf. Kuhn and East, *J. Sci., Instr.*, **1946**, **23**, 185) and a detachable weighing tube. Uranium hexafluoride was introduced into the bulb and, after 30 min. had been allowed for temperature equilibrium to be attained, the pressure was recorded and then decreased by surrounding the weighing tube with solid carbon dioxide–alcohol. Results were as follows:

Temp.	18·0°	56·0°	83·0°	96·0°
Pressure range, mm.	1·76—17·90	0·89—18·22	0·31—1765	0·03—1090
Mean value of *M*	352 ± 1	352 ± 1	352 ± 1	352 ± 1

Vapour Pressure (−15° to 100°).—(*a*) The vapour pressure between 0° and 100° was measured by means of the apparatus shown in Fig. 2. The glass bulb 9 was connected to the inside of the bellows through a copper–glass seal, and the connecting tube wound with nichrome wire and well lagged. After being thoroughly degassed, uranium hexafluoride was distilled into the bulb, which was then sealed off. The temperature of the manometer and connecting tube

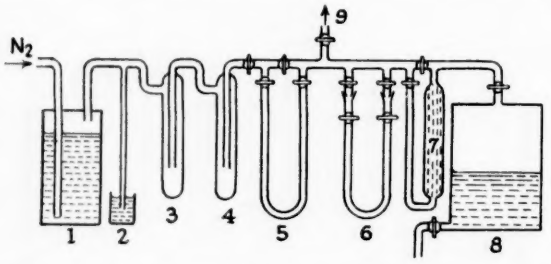


FIG. 3.

1, *Sulphuric acid bubbler.*
2, *Safety bubbler.*
3 *and* 4, *Liquid-air traps.*
5, U-*Tube containing* UF_6.
6, *Detachable* U-*tube.*
7, P_2O_5 *guard tube.*
8, *Aspirator.*
9, *To pumps and main* UF_6 *reservoir.*

was raised to 100° and kept thereat for about 1 hour before measurement of the external pressure corresponding to the make and break of the electrical circuit. The determinations were carried out with frequent changes of hexafluoride. Results are appended:

Temp.	Press., mm.	Temp.	Press., mm.	Temp.	Press., mm.	Temp.	Press., mm.	Temp.	Press., mm.
0·0°	17·9	20·5°	83·1	46·2°	423·4	69·7°	1338	83·5°	1970
5·3	27·4	24·6	109·6	50·0	520·2	70·0	1350	85·0	2058
7·9	32·9	30·8	164·4	54·1	656·2	72·8	1470	89·3	2300
10·0	39·2	32·5	196·2	58·0	806·2	75·0	1566	95·0	2648
13·3	49·6	37·6	251·2	62·9	1042	79·1	1752	100·0	2985
18·7	73·1	43·0	356·0	64·8	1161	82·0	1905		

Values at each degree from 0° to 65° and from 65° to 100° are given on p. 35.

(*b*) Between 0° and −15° the vapour pressure was measured by a dynamic method. The apparatus (Fig. 3) was thoroughly degassed, and uranium hexafluoride condensed in the U-tube (5) by slowly immersing it in an ice–water mixture. Dry nitrogen was drawn over the fluoride by running water from the aspirator, and the hexafluoride condensed out and weighed in the U-tube (6). The determination was repeated, for different samples, and different rates of nitrogen flow, with the U-tube (5) at 0° or −15°. The results were:

Temp.	−14·8°	0·0°
V. p., mm.	5·13 ± 0·03 (mean of 5 values)	17·81 ± 0·03 (mean of 5 values)

Critical Temperature.—The hexafluoride was distilled into a Pyrex tube about 10 cm. long and 3 cm. in internal diameter. The sealed-off tube was attached by wire to a thermometer and supported in a heated glass tube. The temperature was slowly increased until all the liquid had disappeared. Successive lengths of 2 cm. were sealed off until it was observed, on raising the temperature, that the meniscus disappeared suddenly from midway up the tube. The temperature of disappearance and reappearance of the meniscus was observed for a number of tubes. The critical temperature was thus found to be 245° ± 5°.

Specific Heat (−60° to +100°).—A copper calorimeter was made from a cylinder, of 8 mm. internal diameter and 5 cm. long, and connection made to it through a copper capillary tube of 1 mm. internal diameter. The calorimeter was covered with a thin layer of insulating material and wound with 2 m. of 36-gauge enamelled Eureka wire; between these turns a platinum wire was wound for measuring temperature. The resistance thermometer was calibrated by surrounding it in turn with solid carbon dioxide, ice, and steam.

The calorimeter was filled with liquid uranium hexafluoride by attaching it through a copper–glass seal to a small re-entrant trap as previously described. Care was taken to see that the temperature of the system was a little above 100°. When full, the copper capillary was squeezed tightly in a vice and the calorimeter allowed to cool. The capillary was cut in the middle of the squeezed portion and both parts were rendered vacuum-tight by a little soft solder. The calorimeter was suspended by its leads in a wide (5 cm.) silvered tube which could be evacuated and surrounded by a thermostat.

The heater circuit was completed through a 4-v. accumulator, a variable resistance, an ammeter, and an automatic time switch. A high-resistance voltmeter was connected across the heater. The procedure was as follows. The calorimeter was brought to the required temperature, and after evacuation of the tube surrounding the calorimeter, the resistance of the platinum thermometer was taken at 1-min. intervals during 10 min.; the heating current

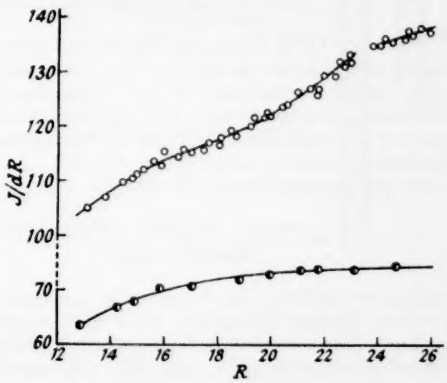


FIG. 4.
○ *Calorimeter and* UF_6.
◐ *Empty calorimeter.*

was then switched on for 4 min., the watts absorbed being obtained from the readings of the voltmeter and ammeter in the heating circuit. At the end of the heating period the resistance of the platinum thermometer was again recorded at 1-min. intervals for 10 min. The effective change in resistance (dR) during the heating period was obtained from a resistance–time graph. Heat exchanges between the calorimeter and its surroundings were estimated from the slope of the curves before and after heating.

When sufficient values of the heat capacity of the full calorimeter had been obtained for temperatures between −60° and 100° it was weighed and then emptied. The heat capacity of the empty calorimeter was determined as before. Graphs were drawn connecting J/dR and R, where J is the input energy in joules corresponding to a change of resistance dR at the mean resistance R.

A subtraction of these curves (Fig. 4) gives a relation between J/dR and R for the sample of hexafluoride alone. From this curve, the weight of hexafluoride used, and the calibration curve for the resistance thermometer, the heat capacity was calculated. A correction was applied for the heat used in evaporating solid or liquid when the calorimeter was not full.

Two further samples of uranium hexafluoride were used. The weight of material used was constant and the results have been plotted together. They are tabulated at round values of temperature on p. 34, the estimated error being ±1%.

Melting Point and Heat of Melting.—The apparatus used was that described in the preceding section. The calorimeter was heated continuously from 20° to 100°. The graph connecting temperature with time showed a horizontal portion corresponding to a m. p. at 64·9°. This temperature was confirmed by heating a sample in a sealed glass tube.

The heat of fusion (4550 cal. mol.$^{-1}$) was calculated from the length of the horizontal portion

and a knowledge of the heat input. Corrections were applied for heat losses due to radiation and conduction along the leads.

Viscosity.—(1) *Liquid* (70—100°). An Ostwald viscometer was sealed on to a small re-entrant trap and filled to two-thirds of its capacity with liquid by the method previously described, then cooled and sealed off. The viscometer was immersed in a glass thermostat and supported by a device which permitted rotation through 180° about a horizontal axis. The bath was kept at 70° for 30 minutes, after which the viscometer was tilted so that liquid flowed into and filled the smaller bulb. It was then returned to the vertical, and the time taken for the liquid to fall between the two predetermined marks was measured. This procedure was repeated at a number of temperatures between 70° and 100°, and after the exact depth of liquid had been marked, the tip was broken off and the viscometer emptied. The constant for the viscometer for the particular quantity of liquid used was determined by repeating the experiment with the same volume of purified alcohol and water. Finally, the determination was repeated with different samples and volumes of uranium hexafluoride. The results were :

Temp.	67·9°	70·0°	71·5°	73·9°	74·5°	76·5°	78·8°
$10^2\eta$ (poises)	0·924	0·910	0·902	0·892	0·880	0·876	0·870
Temp.	83·3°	84·9°	88·3°	92·2°	95·7°	97·8°	99·0°
$10^2\eta$ (poises)	0·834	0·832	0·815	0·794	0·770	0·766	0·752

Values at round temperatures are given on p. 36.

(ii) *Vapour* (0—200°). A Pyrex capillary tube, 17·5 cm. long, was selected for uniform bore. One end was connected through a fine-control bellows-valve to a uranium hexafluoride reservoir and a bellows manometer; the other was also connected to a bellows manometer and through a change-over tap to two small condensing vessels, one of which could be removed from the apparatus and weighed. The capillary was surrounded by a hot-air bath with thermocouples distributed to ensure a uniform temperature.

The viscosity was calculated from the formula

$$\eta = \frac{\pi r^4(p_1^2 - p_2^2)t\rho(1 + 4\xi/r)}{16lm(p_1 + p_2)/2} - \frac{m(1{\cdot}12 + ln p_1/p_2)}{8\pi tl}$$

where r = radius of capillary; $p_1 - p_2$ = the pressure difference between the ends of the capillary; ρ = mean density of vapour; m = mass of vapour flowing in t seconds; l = length of capillary. The " slip " correction ($4\xi/r$), where ξ is approximately equal to the mean free path, at the mean pressure, was less than 1%. The second term was less than 0·5%.

Temp.	20·0°	65·0°	94·0°	128·0°	166·0°
$\eta \times 10^4$ (poises)	1·76 ± 0·03	1·94 ± 0·03	2·08 ± 0·03	2·24 ± 0·03	2·57 ± 0·03

The results, each the mean of 5 measurements, were as follows (values at round temperatures on p. 36) :

Thermal Conductivity. Vapour (5° *and* 105°).—The thermal conductivity was determined by comparing the heat loss from an electrically heated wire confined in a co-axial cylinder, when surrounded by air and by uranium hexafluoride severally. Gregory and Archer (*Proc. Roy. Soc.*, 1926, *A*, **110**, 91) have given equations for the heat loss from two wires, identical in all respects except length. It is shown that two wires of length l_1 and l_2 incorporated in a Callendar–Griffiths bridge as in Fig. 5 may be treated as an ideal length of wire ($l_1 - l_2$) having uniform temperature and no end corrections. The heat loss from this wire may be written as

$$C^2R = 2\pi Kl\theta/\log(r_2/r_1) + \phi + \psi$$

where C = heating current; R, l, and θ = resistance, length, and temperature of wire, respectively; r_1 and r_2 = radius of wire and tube respectively; ϕ = heat loss by convection; ψ = heat loss by radiation; K = thermal conductivity of the surrounding vapour.

Following previous workers, using the hot wire method, ϕ was eliminated by working at pressures sufficiently low for it to be neglected; ψ was determined by measuring the heat loss when the tubes were evacuated. The variable resistance r (Fig. 5) used to balance the bridge corresponds to the length of wire $l_1 - l_2$, so that as long as r remained constant and the bridge balanced, the resistance, and consequently the temperature of the ideal length of wire of length l, remained constant.

If $C_{vac.}$, C_{air}, and C_{UF_6} are the currents necessary to balance the bridge when the tubes are evacuated, or filled with air or with hexafluoride, then the ratio of the conductivities is given by

$$\frac{K_{air}}{K_{UF_6}} = \frac{C_{air}^2R - C_{vac.}^2R}{C_{UF_6}^2R - C_{vac.}^2R}$$

The tubes were made of nickel of $\frac{1}{2}$" internal diam., one 8" long and the other 4" long. The nickel wires were 0·05" in diameter, and insulated from one end of the tube. For temperatures around 0° this could be done by an insulating washer rendered vacuum-tight by Apiezon wax W. For temperatures around 100°, the nickel wire was attached to a tungsten wire sealed through the glass of a copper–glass seal. Great care was taken to ensure that the

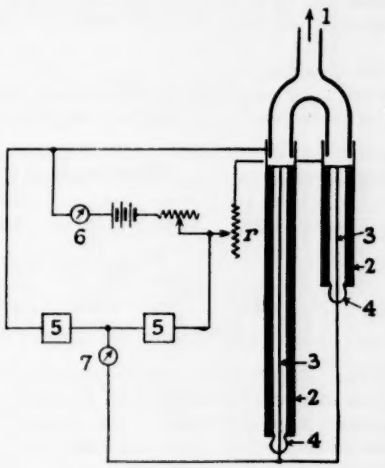


FIG. 5.

1, *To pumps and* UF_6 *reservoir.*
2, *Nickel tubes.*
3, *Nickel wires.*
4, *Tungsten–glass seals.*
5, 5,000 W *resistance.*
6, *Ammeter.*
7, *Galvanometer.*

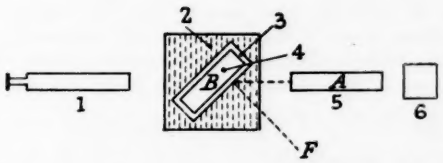


FIG. 6.

1, *Telescope.*
2, *Uranium hexafluoride.*
3, *Glass.*
4, *Air.*
5, *Collimator.*
6, *Slit and source of light.*

size and resistance of the ends were identical, and many pairs were made before the desired similarity was produced.

When full of air at atmospheric pressure, the tubes were surrounded by a thermostat, and, a very small bridge current being used, the value of r to balance the bridge was found for various temperatures of the thermostat between 0° and 120°.

To compare the conductivities of air and uranium hexafluoride the thermostat was set at 0° and r chosen to correspond to a wire temperature of about 10°. The bridge was then balanced by varying the current with the tubes (*a*) evacuated, (*b*) surrounded by air, (*c*) surrounded by hexafluoride. For each condition a series of readings was taken at different pressures. The balancing current increases from $C_{vac.}$ when the tubes are evacuated to a constant value C_{air} or C_{UF_6} which increases only when convectional losses become appreciable.

Measurements were made for different values of r and the thermostat was then raised to 100°. The value of the conductivity of carbon dioxide measured at the lower temperature was within 0·5% of the value reported in the International Critical Tables. Results are given on p. 36.

Refractive Index (*Liquid*, 70—100°).—The methods available for determining the refractive index of liquid uranium hexafluoride were very limited because the properties of the liquid necessitate an apparatus which can be heated above 65° and withstand a pressure of 3 atm. The method which finally proved satisfactory was that involving the optical system shown in Fig. 6. An air cell immersed in the liquid could be rotated about a vertical axis between the telescope and collimator. By rotating the cell at right angles to the beam of light a position

can be reached when the field of vision is divided into light and dark sections. At this point, which is well defined, total internal reflection takes place and it can be shown that μ(air/liq.) = 1/sin *ABF*.

The cell was constructed by fusing together the perimeters of two circular Pyrex glass plates, 1½ mm. thick, and of 2 cm. diameter. A glass tube was sealed to one part of the perimeter, through which the cell could be evacuated and tested for leaks. When free from leaks, the cell was sealed off and supported in the centre of a glass tube, 2½ cm. in diameter, attached to a re-entrant trap. The glass cell was then covered with liquid hexafluoride and, after being cooled and sealed off from the trap, the outer glass tube was mounted in a brass cylinder connected through a universal joint to a vernier pointer moving over a horizontal scale. The universal joint was clamped when the cell rotated about its vertical axis. A thermostat with parallel glass sides was brought into position around the tube, and the telescope and collimator adjusted.

Two series of readings were taken, one with a sodium lamp and one with a mercury-vapour lamp and filter. At various temperatures between 70° and 100° the four positions of the cell for which the field of vision was divided were recorded and the refractive index calculated.

Wave-length of light 5890 Å.

Temp.	69·4°	72·2°	73·5°	77·5°	85·2°	87·2°	90·5°	95·1°
μ	1·367	1·366	1·367	1·360	1·353	1·354	1·350	1·347

Wave-length of light 4360 Å.

Temp.	66·0°	68·0°	72·3°	75·2°	79·2°	84·0°	84·7°	90·5°	91·0°
μ	1·385	1·386	1·382	1·377	1·376	1·371	1·369	1·364	1·364

Values at round temperatures are given on p. 36.

Surface Tension (70—100°).—The ends of two similar Pyrex capillary tubes and a third tube of narrow diameter (0·5 mm.) were connected together with two pieces of wide-bore tubing, sealed to a small re-entrant vessel. The diameters of the tubes were found by measuring the capillary rise in each of (*a*) pure redistilled alcohol and (*b*) ether. The apparatus was then filled with liquid hexafluoride in the usual way. The differences in heights between the hexafluoride meniscus in (i) each of the two capillary tubes and (ii) the third tube were determined at different temperatures, from which values of the surface tension were calculated.

The contact angle was determined by pouring liquid hexafluoride on a flat glass plate in an evacuated vessel. The angle was too small to be measured, and the correction for the shape of the meniscus was taken to be zero.

The values obtained are given on p. 36.

Discussion

Molecular Weight.—Found: 352 ± 1. Calc.: 352·1. Amphlett, Mullinger, and Thomas (*loc. cit.*) obtained a similar value for measurements up to 50° over a pressure range of 5—500 mm.

Critical Data.—Critical temperature = 245° ± 5°. The value calculated from the Ramsay–Shields equation and the measured values of the surface tension is 235° ± 20°. On the assumption that at the critical temperature the viscosities of liquid and vapour are equal, this temperature is again found to be 235°. In view of the large extrapolations involved these values are not very significant.

Triple-point Data.—These are found to be: temperature (p. 31), 64·9°; vapour pressure (p. 30) 1161 mm.; density of liquid (p. 30), 3·63 g. cm.$^{-3}$; heat of fusion (p. 31), 4550 cal. mol.$^{-1}$.

Specific Heat.—The values for the solid agree with those reported by Brickwedde, Hoge, and Scott (*J. Chem. Phys.*, 1948, **16**, 429) at −50° and +30° but there is a maximum

Temp.	−50°	−40°	−20°	0°	20°	40°	60°	70°	80°	90°	100°
C, cal. mol.$^{-1}$ deg.$^{-1}$	34·2	34·6	35·7	37·0	39·0	41·8	44·5	47·4	48·1	48·8	49·5

difference of ~5% at 60°. The values for the liquid are in poor agreement and differ by about 5% at 100°, which is large even when the difficulties of handling the material are taken into consideration.

The specific heat of the gas was measured by H. S. Arms (personal communication) and the following values were obtained :

Temp.	25°	75°	125°
C_p, cal. mol.$^{-1}$ deg.$^{-1}$	33·5 ± 1	34·5 ± 1	35·3 ± 1

Values calculated from an analysis of the infra-red spectroscopic data (Bigeleisen and Mayer, *J. Chem. Phys.*, 1948, **16**, 443) are lower by 5% and extend over a larger temperature range. From Arms's values, extrapolated with the help of the spectroscopic data, the following values have been obtained :

$$C_p \text{ (solid)} - C_p \text{ (vapour)} = (e^{-2560/T} + 21{\cdot}53)/T^2 + 2 \text{ cal. mol.}^{-1} \text{ deg.}^{-1}$$
$$C_p \text{ (liquid)} - C_p \text{ (vapour)} = 0{\cdot}045T - 1{\cdot}85 \text{ cal. mol.}^{-1} \text{ deg.}^{-1}$$

Vapour Pressure.—(i) The vapour pressure of the solid at $T°$ K is given by

$$\log P = \int_0^T \frac{\lambda_0}{RT^2}\,dT - \int_0^T \frac{dT}{RT^2}\int_0^T \left(\frac{e^{-2560/T} + 21{\cdot}53}{T^2} + 2\right)dT$$

where λ_T = heat of vaporization of the solid at $T°$/K. Integrating, and calculating the values of the integration constants from the measured values of temperature and pressure, we get

$$\log_{10} P_{\text{mm.}} = -2751/T - 75{\cdot}0\, e^{-2560/T} - 1{\cdot}01 \log_{10} T + 13{\cdot}797$$

Vapour pressure, mm.

Temp.	0°	−1°	−2°	−3°	−4°	Temp.	0°	−1°	−2°	−3°	−4°
−15°	5·00	4·52	4·12	3·76	3·42	−5°	11·9	10·9	10·0	9·18	8·43
−10	7·73	7·08	6·49	5·93	5·42	0	17·9	16·5	15·2	14·0	12·9

Temp.	0°	1°	2°	3°	4°	Temp.	0°	1°	2°	3°	4°
0°	17·9	19·4	21·0	22·8	24·6	35°	215	229	244	259	275
5	26·6	28·8	31·1	33·5	36·1	40	292	310	330	350	371
10	39·0	42·0	45·2	48·6	52·4	45	394	417	442	468	494
15	56·2	60·4	64·9	69·7	74·8	50	522	552	583	617	652
20	80·2	85·9	92·0	98·6	105·4	55	689	726	766	807	851
25	112·7	120·5	128·8	137·7	146·9	60	897	946	998	1047	1104
30	157	167	178	190	202	65	1161				

(ii) By a similar procedure the following equation has been derived for the vapour pressure of the liquid :

$$\log_{10} P_{\text{mm.}} = -1946/T - 0{\cdot}00492T + 0{\cdot}934 \log_{10} T + 8{\cdot}123$$

Vapour pressure, mm.

Temp.	0°	1°	2°	3°	4°	Temp.	0°	1°	2°	3°	4°
65°	1161	1190	1235	1270	1310	85°	2050	2105	2160	2220	2280
70	1350	1390	1430	1480	1520	90	2330	2390	2460	2520	2580
75	1560	1610	1650	1700	1750	95	2650	2710	2780	2840	2910
80	1790	1840	1890	1950	2000	100	2980				

Values for the vapour pressure of the solid from 12° to 50° reported by Amphlett, Mullinger, and Thomas (*loc. cit.*) lie on either side of the formula values but do not show the deviation from the linear relation between log p and $1/T$. Those reported by Crist and Weinstock (*J. Chem. Phys.*, 1948, **16**, 436) agree within 1·5%, their data lying above the formula values.

Latent Heats.—Heat of sublimation (solid). Calculated from specific-heat and vapour-pressure measurements by the following formula, these are found to be :

$$\lambda_T = 12{,}600 - 875{,}600\, e^{-2560/T} - 2T \text{ cal. mol.}^{-1}$$

Temp.	−50°	−25°	0°	20°	40°	60°	65°
λ_T, cal. mol.$^{-1}$	12,145	12,075	11,980	11,870	11,730	11,530	11,470

Estimated error = ± 1%.

Heat of evaporation (liquid). The formula deduced from specific-heat and vapour-pressure measurement is

$$\lambda_T = 8890 - 0{\cdot}0225T^2 + 1{\cdot}85T \text{ cal. mol.}^{-1}.$$

This formula does not satisfy the condition that $\lambda_T = 0$ at the critical temperature and the empirical formula

$$\lambda_T = 6920 - 5{\cdot}3(t - 65) - 0{\cdot}184(t - 65)^2 \text{ cal. mol.}^{-1}$$

where t is the centigrade temperature, has been obtained which agrees with the first formula over the measured range and does satisfy the condition that $\lambda_T = 0$ at 245°. The results (estimated error ±1%) are :

Temp.	65°	70°	90°	110°
λ_T, cal. mol.$^{-1}$	6920	6890	6670	6310

The heats of sublimation and evaporation have been measured by Masi (*J. Chem. Phys.*, 1949, **17**, 755) and values for the solid are within 1% of those calculated above; those for the liquid differ by 2% at 100°. The values at the triple point are 11,429 and 6859 cal. mol.$^{-1}$, giving 4570 cal. mol.$^{-1}$ for the heat of fusion, in excellent agreement with the value 4550 ± 50 cal. mol.$^{-1}$ reported on p. 31.

Density.—Liquid. Values at round temperatures are :

Temp.	65°	70°	80°	90°	100°
d, g. cm.$^{-3}$	3·63	3·60	3·54	3·48	3·41

The density at the triple point was found by H. F. Priest (OSRD Report, A 139) to be 3·607 g. cm.$^{-3}$. The density has also been measured by the falling-drop method (Hoge and Wechsler, *J. Chem. Phys.*, 1949, **17**, 617) and the values reported are within 0·5% of those given above. At the triple point the value by this method is 3·624 g. cm.$^{-3}$.

Viscosity.—Liquid. Values at round temperatures (estimated error ± 1%) are :

Temp.	70°	80°	90°	100°
$10^3\,\eta$ (poises)	9·1	8·5	8·0	7·5

Vapour. $\eta = 1{\cdot}67(1 + 0{\cdot}0026t) \times 10^{-4}$ poise (±2%)

Temp.	0°	20°	50°	100°	150°	200°
$10^4\,\eta$ (poises)	1·67	1·76	1·89	2·11	2·33	2·55

Sutherland's constant calculated from these data is 101. The mean free path at 0° is $1{\cdot}27 \times 10^{-3}$ cm. at 1 mm.

Thermal Conductivity of Vapour.

Temp.	5°	105°
$K \times 10^5$, cal. deg.$^{-1}$ cm.$^{-1}$ sec.$^{-1}$	1·42	1·94

Estimated error = ± 1%.

Surface Tension.—The parachor, based on the following values, is 200 ± 1.

Temp.	70°	80°	90°	100°
γ, dyne cm.$^{-1}$	16·8	15·6	14·3	13·1

Estimated error = ± 1%.

Refractive Index.—Liquid. Values at round temperatures are :

Temp.	70°	80°	90°	100°
μ at 4360 Å	1·383	1·374	1·365	1·355
μ at 5890 Å	1·367	1·358	1·350	1·342

From these values the molecular refraction is : $[R]^{85}_{4360} = 22{\cdot}59 \pm 0{\cdot}1$, $[R]^{85}_{5890} = 21{\cdot}83 \pm 0{\cdot}1$.

Vapour. Calculated on the assumption that the molecular refraction of the vapour is the same as that of the liquid, the index of refraction of the vapour is given by $n - 1 = 5{\cdot}2 \times 10^{-4} p/T$, where p is pressure in mm. and T the absolute temperature.

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6. *The Upper Limits of Inflammability of Hydrogen–Air and Hydrogen–Nitrous Oxide Mixtures.*

By S. Smith and J. W. Linnett.

The compositions of the hydrogen–air and hydrogen–nitrous oxide mixtures at the upper limit of inflammability have been determined for upward propagation in a vertical tube 150 cm. long and 5 cm. in diameter, open to the atmosphere at the lower end. The effect of varying the proportion of air to nitrous oxide on the percentage of hydrogen in the hydrogen–air–nitrous oxide limit mixtures has been determined; and the effects of the addition of nitrogen, methyl alcohol, and methyl iodide on the composition of the hydrogen–air and hydrogen–nitrous oxide limit mixtures, and of ethyl alcohol on the composition of hydrogen–air limit mixtures, have been studied. Some limit flame temperatures have been calculated. It is concluded that the differences in behaviour observed can be related (*a*) to the difference between the hydrogen–oxygen and hydrogen–nitrous oxide chain reactions, the former being branching and the latter non-branching, and (*b*) to the difference between the limit flame temperatures of the two mixtures, which appears to be a consequence of the difference between the chain reactions.

Dixon-Lewis and Linnett (*Proc. Roy. Soc.*, 1951, **210**, *A*, 48) described observations on the effects of small amounts of organic material on the upper limit of inflammability of hydrogen–air mixtures. They found, as had Tanaka and Nagai (*Proc. Imp. Acad. Japan*, 1926, **2**, 280, 283, 494, *et seq.*), that the graph of percentage of hydrogen at the limit against percentage of organic vapour added, was not a single straight line; *i.e.*, Le Chatelier's rule was not obeyed. The graphs in fact consisted of two parts: the first small additions caused a large fall in the percentage of hydrogen at the limit, but further addition had proportionately less effect. Thus, the first part of the graph had a greater slope than had the second part. Moreover, the latter obeyed a modified form of Le Chatelier's rule, *i.e.*, it was a straight line. They interpreted their results in terms of the known chain-branching character of the hydrogen–oxygen reaction, and the large effect of the first small additions was regarded as being the result of chain-breaking by the organic molecules. This effect is possible because the upper limit flame temperature of hydrogen–air mixtures is much less than those of most organic vapour–air mixtures, so that the organic molecules are then relatively unreactive. With further addition the limit flame temperature rises to compensate for this chain-breaking effect, and at some point the limit flame temperature of the organic molecule is reached and its oxidation contributes to the combustion. Its lowering effect on the hydrogen percentage at the limit is then much less, so that the slope of the graph for further additions beyond this becomes less.

The object of the present work was to compare the limit of hydrogen–air mixtures with that of hydrogen–nitrous oxide mixtures, and the effect of added materials on these limits. These mixtures were chosen because it is known that the hydrogen–oxygen reaction is a branching-chain reaction whereas the hydrogen–nitrous oxide reaction is a non-branching chain reaction. A comparison of the behaviour of the limits might, therefore, elucidate the factors governing the composition of limit mixtures.

Egerton and Powling (*Proc. Roy. Soc.*, 1948, **193**, *A*, 172, 190) made extensive measurements of inflammability limits including those of hydrogen–air and hydrogen–nitrous oxide mixtures. However, they studied mainly the lower limit. Their results are discussed on p. 41.

Posthumus (*Rec. Trav. chim.*, 1930, **49**, 309) determined the upper limit of inflammability of hydrogen–nitrous oxide mixtures, by using a closed tube of diameter 1·6 cm. We found that mixtures well outside the limit given by him carried a flame. Possible explanations for this will be considered later.

Experimental

The combustion tube in which the inflammability of the prepared mixtures, as regards upward propagation, was tested, was 150 cm. long and 5 cm. in diameter. It was closed

initially at both ends by ground-glass plates fitting on the flanged ends of the tube. Platinum sparking electrodes were sealed into side arms at the lower end of the tube by means of vacuum wax, the width of the spark gap being 2—3 mm. Sparking was effected by a $2\mu F$ condenser charged to about 4000 volts. Ignition was always at room temperature ($17° \pm 3°$) and atmospheric pressure, the lower ground-glass plate being removed from the end of the tube immediately before ignition. The criterion for flame propagation was that a flame should reach the top of the combustion tube. In some cases the flames were scarcely visible, and propagation was observed by means of a copper–constantan junction waxed into a side tube at the top of the combustion tube and connected to a microammeter.

It is important that the spark should be powerful enough to ignite the mixture being tested. Under our conditions, even when the flame did not propagate to the top of the tube, a diffusion flame of hydrogen in the outside air always burned at the lower end of the tube after the spark had passed. Further proof that the spark was sufficiently powerful was obtained by comparing the limit obtained when ignition was by spark and when it was effected by a small coal-gas flame drawn across the mouth of the tube immediately the plate was removed. The limits obtained by the two methods for mixtures of hydrogen and nitrous oxide containing 1% of methyl alcohol were identical. Two limits for mixtures of hydrogen, nitrous oxide, and methyl alcohol were determined with use of flame ignition, the rest being determined with spark ignition; all fell on a smooth curve. There is, therefore, little doubt that the limits determined were independent of the ignition source.

The gas mixtures were made up in a 5-l. all-glass spherical vessel. Complete mixing was ensured by causing a long glass plate to swing back and forth inside the vessel by means of an electromagnetic device. The hydrogen–air upper limit was determined (*a*) after 300, (*b*) after 500 complete swings of the plate, and (*c*) as in (*b*) but after the mixture had been left overnight. The limits obtained after treatments (*a*), (*b*), and (*c*) were identical. During the remainder of the work procedure (*a*) was adopted.

The partial pressures of the various gases in the mixtures were measured on a mercury manometer. When a small proportion of any material was required, a higher pressure of it was measured in a subsidiary vessel and the gas then expanded into the mixer. The ratio of the initial and the final pressure for this expansion was measured in a separate experiment at higher pressures.

The procedure in determining the inflammability of a mixture was as follows. The 5-l. mixing volume and the 3-l. combustion tube were evacuated by a mercury-vapour pump backed by a rotary oil pump. The gases were then measured in the 5-l. volume and mixed with a Töpler device, they were transferred to the combustion tube until the pressure in the tube was about 5 mm. above atmospheric. The lower plate was removed, and the igniting spark passed. The passage or non-passage of flame up the tube was then noted. This process was then repeated with mixtures of varying composition until the limit had been fixed sufficiently accurately. The following figures demonstrate that it is possible to fix the limit composition, in favourable circumstances, to closer than 0·1%. For hydrogen–air mixtures the following set was obtained (percentages refer to H_2; F = flame propagated in the mixture, NF = no propagation): 74·67, NF; 74·64 NF; 74·52 F; 74·59 F; 74·56 F; 74·69 NF; 74·56 F; 74·67% NF. The limit was therefore taken to be 74·62% of hydrogen. Egerton and Powling (*loc. cit.*) determined this limit in a tube 150 cm. long and 5·3 cm. in diameter and found the upper limit composition to be 74·6% of hydrogen. The agreement is excellent.

Cylinder hydrogen was used; it was freed from oxygen by passage through a silica-tube furnace packed with platinised asbestos and heated electrically to about 800°. The water formed was removed by passing the gases from the furnace through a trap cooled in liquid air. Cylinder nitrogen was used; it was freed from the 1—2% of oxygen it contained by passing the gas up a long tower packed with pumice over which trickled an alkaline solution of sodium dithionite (hydrosulphite) containing sodium anthraquinone-β-sulphonate. The gas was dried by passing it through a trap cooled in liquid air. Nitrous oxide, also from a cylinder, was condensed in a trap cooled in liquid air, then degassed by liquefaction, and resolidified, and the space above it was re-evacuated. This was repeated until no further degassing took place. The nitrous oxide was stored as solid in the trap, and when it was required the liquid air was removed and a portion of the oxide evaporated into the mixer. Mixtures containing nitrous oxide behaved reproducibly even though some were made up with nitrous oxide evaporated from the first and some from the last part of a sample in the trap. This indicates that the nitrous oxide was not contaminated with nitrogen or oxygen. Air was passed into the apparatus through a trap cooled in liquid air so that it was freed from water and other condensable impuri-

ties. The methyl alcohol was dried by boiling it with 5% of solid potassium hydroxide; it was then distilled, kept overnight over freshly burnt quicklime, and redistilled; the fraction of b. p. 64·5—65° was used. The ethyl alcohol was dried by the same method, and the fraction, b. p. 78—78·5°, used. The alcohol was stored in a bulb attached to the vacuum line. Before use, it was solidified in liquid air, and the bulb evacuated. It was then allowed to melt and the cycle repeated until no further degassing occurred. The methyl iodide was first shaken with a little mercury to remove iodine, then distilled *in vacuo* into the storage bulb and subjected to the same degassing treatment as the methyl alcohol.

Results.—The upper limit compositions for hydrogen–air and hydrogen–nitrous oxide mixtures are 74·62% and 83·91% of hydrogen, respectively. The limiting compositions for various hydrogen–nitrous oxide–air mixtures are given in Table 1. The calculated flame temperatures of the limit mixtures are also included; these were calculated by using the data of Lewis and von Elbe and of Dwyer and Oldenberg and assuming that the products were at equilibrium at the flame temperature.

TABLE 1.

Air in oxidising gas, %	0	20	40	60	80	100
H_2 at limit, %	83·91	83·40	82·07	80·03	77·39	74·62
Calc. flame temp., °c	1617°	1477°	1368°	1248°	1122°	913°
Diff.		140°	109°	120°	126°	209°

The upper limit compositions obtained when small amounts of methyl alcohol, ethyl alcohol, and methyl iodide, and larger amounts of nitrogen were added to hydrogen–air mixtures, are given in Table 2, those for additions to hydrogen–nitrous oxide mixtures in Table 3.

TABLE 2. *Upper limit compositions of some hydrogen–air–additive mixtures.*

MeOH, %	H_2, %	Air, %	EtOH, %	H_2, %	Air, %	MeI, %	H_2, %	Air, %	N_2, %	H_2, %	Air, %
0·51	71·97	27·52	0·22	70·26	29·52	0·52 *	61·30	38·18	10·90	64·00	25·10
0·97	68·90	30·13	0·51	64·61	34·88	1·00	53·43	45·57	30·00	45·11	24·89
1·71	65·66	32·63	0·72	63·50	35·78	2·03	44·06	53·91	40·04	35·36	24·60
2·92	59·72	37·36	1·47	57·74	40·79	3·48	34·20	62·32			
3·81	54·80	41·39	2·52	50·45	47·03	4·95	26·87	68·18			
5·45	49·40	45·15	4·02	42·00	53·98						
6·90	47·15	45·95									
8·04	44·63	47·33									

* Result obtained by Egerton and Powling (*loc. cit.*).

TABLE 3. *Upper limit compositions of some hydrogen–nitrous oxide–additive mixtures.*

MeOH, %	H_2, %	N_2O, %	MeI, %	H_2 %	N_2O, %	N_2, %	H_2, %	N_2O, %
0·52	82·23	17·25	0·50	80·76	18·74	10·10	73·94	15·96
0·99	80·83	18·18	0·99	78·95	20·06	20·10	64·64	15·26
2·54	78·53	18·93	2·04	76·61	21·35	35·01	50·14	14·85
4·13	75·70	20·17	3·52	75·06	21·42	50·02	35·22	14·76
6·03	72·98	20·99	4·97	73·99	21·04			
8·06	69·95	21·99						

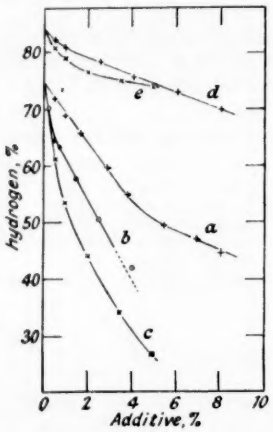
In the figure the results for methyl alcohol, ethyl alcohol, and methyl iodide are shown graphically. These curves show that Le Chatelier's rule fails for these mixtures. The graphs of contents of hydrogen against added nitrogen in the limit mixtures are linear for both hydrogen–air–nitrogen and hydrogen–nitrous oxide–nitrogen mixtures. Other interesting features are the following:

(*a*) As methyl iodide is added to hydrogen–nitrous oxide mixtures the percentage of nitrous oxide in the limit mixtures increases at first, but for amounts of methyl iodide greater than 3% it falls again. Thus over the range 3—5% of methyl iodide the percentages of both hydrogen and nitrous oxide are decreasing as the methyl iodide increases. This result was so surprising that the limit for mixtures containing 4·97% methyl iodide was redetermined, but verified. No such effect is obtained as methyl iodide is added to hydrogen–air mixtures over the range studied.

(*b*) The percentage of air, as well as that of hydrogen, decreases as the percentage of nitrogen added is increased. The same behaviour is observed for hydrogen–nitrous oxide mixtures. For the air mixtures the air content at the limit falls from 25·4 to 24·6 as the added nitrogen is increased from 0 to 40%. For the nitrous oxide mixtures the percentage of nitrous oxide falls

from 16·1 to 14·9 over the same range. This may be restated as follows: when the percentage of hydrogen is equal to that of the added nitrogen the limit is at 24·7% of air for the air mixtures (0·7% less than in the absence of nitrogen) and 14·8% of nitrous oxide for the nitrous oxide mixtures (1·3% less than in the absence of nitrogen). It appears that the addition of nitrogen has more effect in reducing the amount of oxidising component with the nitrous oxide mixtures. This is true whether one considers absolute or fractional reduction in the proportions of the oxidising component.

(*c*) Tanaka and Nagai (*loc. cit.*) and Dixon-Lewis and Linnett (*loc. cit.*) determined the effect on the upper limit of hydrogen–air mixtures of the addition of members of homologous series of organic compounds, and found that the slope of the first section of the limit graph increased as the series was ascended and that the graph changed slope at a progressively lower percentage addition as the molecular size increased. Our results for the upper limits of hydrogen–air–methyl alcohol and hydrogen–air–ethyl alcohol mixtures are of the same general form as would be expected from these observations. However, they also found that extrapolations of the second sections of the limit graphs of a given homologous series all intercepted the hydrogen axis at the same point. Tanaka and Nagai also found that the second sections of the limit graphs obeyed a modified form of the Le Chatelier rule, the upper limit of the organic vapour–air mixtures and the intercept made on the hydrogen axis being used as the constants. From



Effect of organic additives on H_2*–air and* H_2–N_2O *upper limits.*

(*a*) H_2 + air + MeOH;
(*b*) H_2 + air + EtOH;
(*c*) H_2 + air + MeI;
(*d*) H_2 + N_2O + MeOH;
(*e*) H_2 + N_2O + MeI.

the figure it can be seen that the second sections of the limit graphs obtained in this work for hydrogen–air–methyl alcohol and hydrogen–air–ethyl alcohol mixtures do not intercept the hydrogen axis at the same point. On using White's values (*J.*, 1919, **115**, 1462) for the upper limit compositions of the alcohol–air mixtures (36·5 and 18·95% of the respective alcohols) it is found that the second section of the methyl alcohol graph obeys Le Chatelier's rule as modified by Tanaka and Nagai but the second section of the ethyl alcohol graph does not. On account of these unexpected results the upper limit compositions of mixtures containing 1·5% and 2·54% of ethyl alcohol respectively were redetermined some 8 months after the original observations but were confirmed.

Discussion

It has been possible to check our results against those obtained by Egerton and Powling with a similar tube for hydrogen–air, hydrogen–air–methyl iodide, and hydrogen–nitrous oxide–nitrogen mixtures. In all cases the agreement is good. However, our limit for hydrogen–nitrous oxide mixtures does not agree with that given by Posthumus. He reported that in his closed 1·6-cm. tube, flame was always propagated in mixtures containing less than 75% but never in those with more than 77% of hydrogen. In mixtures containing intermediate amounts flames were sometimes propagated and sometimes not. Because a narrower tube was used by Posthumus it would be expected that his limit would be at a lower percentage of hydrogen than ours. However, the difference is surprisingly large and it may be that his induction coil spark was insufficient to ignite mixtures near the limit.

The lack of reproducibility suggests that this was the case. The limit was entirely reproducible under our conditions.

The calculated limit flame temperature of hydrogen–nitrous oxide mixtures is 1617° while that of the hydrogen–air limit flame is 913°; the difference is surprisingly large. A mixture of hydrogen and nitrous oxide at atmospheric pressure would explode thermally in an isothermally heated vessel at about 700°, while a hydrogen–air mixture would, under the same conditions, explode at about 600°. The former would be a thermal explosion, while the latter would depend on chain branching. The difference of temperature between these explosion limits is much less than that between the calculated flame temperatures of the two limit mixtures. Dixon-Lewis and Linnett concluded from their experiments that the limit was determined by the necessity of reaching a temperature at which a sufficient rate of radical multiplication was allowed. The need for this was supposed to arise because the reaction in any layer must become self-sustaining and at the same time provide a supply of radicals for diffusion into the next layer. Because of its rapid chain-branching mechanism, the hydrogen–oxygen reaction is ideally suited for providing a sufficiently speedy multiplication of radicals in the flame zone at a temperature not much greater than that at which it would explode in a closed vessel. However, the only way in which the number of radicals can increase in the hydrogen–nitrous oxide mixture is by the dissociation of nitrous oxide as a result of a rising temperature. In the hydrogen–oxygen reaction the available energy is used initially to increase the number of radicals, whereas in the hydrogen–nitrous oxide reaction it is initially used to raise the temperature and only secondarily, as a consequence, to increase the number of atoms and radicals. The higher limit flame temperature of hydrogen–nitrous oxide mixtures than of similar hydrogen–air mixtures, therefore, seems to support the view that the multiplication of radicals in the flame front is necessary for the propagation of the flame, and also that the lower the temperature at which this can be achieved at a sufficient speed, the lower will be the minimum temperature necessary for a flame to be maintained (cf. Van Tiggelen, *Bull. Soc. chim. Belg.*, **1946**, **55**, 202; **1949**, **58**, 259).

Egerton and Powling have shown, by comparing the limits of hydrogen–oxygen–helium and hydrogen–oxygen–argon mixtures, that an increase in the thermal conductivity of the mixture makes an increase in the limit flame temperature necessary. This factor will also be operative in causing the limit flame temperature of hydrogen–nitrous oxide mixtures to be greater than that of hydrogen–air mixtures since there is more hydrogen in the former mixture. This, however, could hardly explain the large difference in the limit flame temperatures.

The calculated limit flame temperatures of hydrogen–nitrous oxide–air mixtures (Table 1) show some interesting features. The rises in flame temperature caused by replacing air by nitrous oxide are 209°, 126°, 120°, 109°, and 140° for 20, 40, 60, 80, and 100% replacement, respectively. The most noticeable effect is the relatively large rise in temperature caused by the first introduction of nitrous oxide. A possible explanation of this is that at about 1000°, nitrous oxide slows up the chain-branching process of the hydrogen–oxygen reaction by providing the non-branching reaction

$$N_2O + H = N_2 + OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

as an alternative to the branching reaction

$$O_2 + H = OH + O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

This would decrease the rate of radical multiplication so that the minimum flame temperature would have to rise.

The replacement of the first 20% of nitrous oxide by air causes a greater lowering of the flame temperature (140°) than that of the second 20% (109°). This occurs despite the fall in available oxygen (as compared with upper limit hydrogen–nitrous oxide mixtures) and the fact that the percentage of hydrogen is reduced less in replacing the first 20% than the second 20%. This may be related to Melville's kinetic observation (*Proc. Roy. Soc.*, **1933**, **142**, *A*, 524; **1934**, **144**, *A*, 737) that the addition of oxygen increases the rate of the

hydrogen–nitrous oxide reaction, probably because reaction (2) occurs to some extent, causing an increase in the number of radicals.

These comments on the limits and limit flame temperatures of hydrogen–nitrous oxide–air mixtures are necessarily tentative. The main interest in the results lies in the fact that neither the limits nor the limit flame temperatures change regularly with the proportion of air in the oxidising gas. Moreover, the effects of both the first replacements of nitrous oxide by air and of air by nitrous oxide seem to be much greater than the effects of further replacements in either direction.

The effect of nitrogen on both limits was summarised on p. 39. The fact that both graphs are linear is consistent with the conclusion that nitrogen behaves entirely as an inert gas. The greater effect of nitrogen on the hydrogen–nitrous oxide limit than on the hydrogen–air limit remains to be considered. As nitrogen is added to these mixtures one can say that, to a first approximation, the effect of replacing hydrogen by nitrogen in the upper limit mixture is being studied, for the proportion of air or nitrous oxide changes only slightly. The effect of this replacement is that the thermal conductivity decreases greatly and the diffusion coefficient also decreases, but not to proportionally as great an extent. These effects on the thermal conductivity and diffusion coefficient explain why, as nitrogen is added, less of the oxidising component is required in the limit mixture, *i.e.*, the calculated limit flame temperature can be lower. These observations link up with those of Egerton and Powling (p. 41). It seems probable that the reason why the effect on the hydrogen–nitrous oxide limit is greater is that the multiplication of radicals in that system must be essentially thermal in character, since it can only occur as a result of a rising temperature leading to the necessary dissociation of nitrous oxide to give oxygen atoms. This is the reason why the limit flame of hydrogen–nitrous oxide is hotter than that of hydrogen–air mixtures, and it is probably also the reason why changing the thermal conductivity by replacing hydrogen with nitrogen has a greater effect in the former than in the latter mixtures.

The dual nature of the effect of organic materials on the upper limit of hydrogen–air mixtures, observed by Tanaka and Nagai and by Dixon-Lewis and Linnett, is confirmed by our experiments with alcohols. The curves showing the effects of the alcohols (see fig.) are segmented. A possible explanation of this was given by Dixon-Lewis and Linnett (see p. 37). The effect of methyl alcohol on the hydrogen–nitrous oxide limit is rather different; the first segment is much reduced in length and for amounts of methyl alcohol greater than 1% the curve is linear. With hydrogen–air mixtures it is only for amounts of methyl alcohol greater than 5% that the second segment occurs. This difference is presumably to be related to the difference between the two limit flame temperatures and the fact that the limit flame temperatures of methyl alcohol–nitrous oxide and hydrogen–nitrous oxide mixtures are closer than those of methyl alcohol–air and hydrogen–air mixtures. At the hydrogen–air limit stripping reactions, such as $CH_3{\cdot}OH + H = CH_3 + H_2O$ or $CH_3{\cdot}OH + H = CH_2{\cdot}OH + H_2$, probably reduce (or delay) the rate of chain branching because a reactive radical is replaced by another which is much less reactive at the operative temperature. It appears that with hydrogen–nitrous oxide mixtures there is a slight inhibiting effect for small additions of methyl alcohol but this is only noticeable for amounts less than 1%. For amounts greater than this a straight-line plot is obtained, indicating that the two reactions are occurring side by side without any specific interference, *i.e.*, a modified Le Chatelier rule is obeyed.

For hydrogen–air mixtures, methyl iodide has a much greater effect on the proportion of hydrogen at the limit than does methyl alcohol. The most likely explanation of this lies in the large effect of iodine in reducing the rate of the reaction between hydrogen and oxygen, owing to removal of hydrogen atoms by iodine and its compounds. Our observations confirm those made by Dixon-Lewis and Linnett with a narrow tube. However, with hydrogen–nitrous oxide mixtures, methyl iodide has only a slightly greater effect on the limit than has methyl alcohol, perhaps because iodine is less active in the effective removal of hydrogen atoms at the higher than at the lower temperature. Another possibility is that the removal of hydrogen atoms in the hydrogen–oxygen reaction interferes with the branching chain which is necessary for radical multiplication. In the hydrogen–nitrous oxide

reaction, radical multiplication only occurs with increasing temperature and consequent dissociation of nitrous oxide. The removal of hydrogen atoms does not, therefore, involve so direct an interference with radical multiplication although, of course, it will have some effect by slowing the non-branching chain reaction and hence the rate of temperature rise.

The strange effect summarised in para. (*a*) (p. 39) appears to indicate that in some way the addition of methyl iodide contributes to the flame propagation when large amounts are added. One possible way in which this might happen appears to be that the reaction $CH_3I + H_2 = CH_4 + HI$ might occur. This reaction is exothermic to the extent of about 10 kcal./g.-mol. and so might increase the heat available to raise the temperature of the gases. It is difficult otherwise to see how the percentages of both hydrogen and nitrous oxide in the limit mixture can fall as methyl iodide is added.

It seems that our results for the effect of ethyl alcohol on the upper limit of hydrogen–air mixtures need extension to higher percentages of ethyl alcohol: this was not possible in our apparatus since the tube could not be heated. The linear segment in the figure, extending from about 1% to about 3% of ethyl alcohol would, if extrapolated, cut the alcohol axis at about 10% of alcohol instead of at the upper limit composition of ethyl alcohol–air mixtures (18·95% of EtOH). It must therefore be presumed that the slope of the graph decreases at some higher percentage of ethyl alcohol: it should be noted that the point representing mixtures containing 4% of ethyl alcohol lies above the line drawn through the points between 1% and 2·5%. Also, evidence for a further change of slope of the graph can be obtained from Dixon-Lewis and Linnett's result, that, in their narrow tube (2 cm.), for methyl alcohol and ethyl alcohol, the segments beyond the bends at about 2% addition extrapolated back to about 60% of hydrogen in both cases. It seems that the bends occur at lower percentages of addition in the narrow tube, *e.g.*, for methyl alcohol, at about 2% in the narrow tube and 5% in the 5-cm. tube. This suggests that the bend observed by Dixon-Lewis and Linnett at about 1·8% of ethyl alcohol in the 2-cm. tube is likely to be beyond the highest percentage (4%) examined by us for ethyl alcohol.

No bend corresponding to that observed by us at about 0·5% in the ethyl alcohol curve seems to be present in the methyl alcohol curve: it may be that the greater probable complexity of the ethyl alcohol curve than of the methyl alcohol curve is a consequence of the greater complexity of the ethyl alcohol molecule. It seems probable that the segment corresponding to that beyond 5% in the methyl alcohol curve has not yet been observed in the ethyl alcohol curve, and that the reason why the straight-line sections in the two graphs do not extrapolate to the same percentage of hydrogen is that they are not corresponding segments. A possible explanation for the sharper initial fall in the ethyl alcohol as compared with the methyl alcohol graph, might be that in ethyl alcohol the C–H bond in CH_2 is weaker than in CH_3 so that a reaction of the type $C_2H_5{\cdot}OH + H = C_2H_4{\cdot}OH + H_2$ can occur more readily with ethyl than with methyl alcohol. In addition, ethyl alcohol, by virtue of its increased size, might be more effective in removing active radicals from the low-temperature hydrogen–air limit flame.

It therefore appears that all the results described can be accounted for in terms of (*a*) the branching and non-branching of the hydrogen–oxygen and hydrogen–nitrous oxide chain reactions, respectively, and (*b*) the higher limit flame temperature of the latter mixtures, which is apparently a consequence of (*a*).

We thank Imperial Chemical Industries Limited and the Royal Society for providing apparatus used during this work.

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7. *Homolytic Aromatic Substitution. Part III.* Ratio of Isomerides formed in the Phenylation of Chlorobenzene. Competitive Experiments on the Phenylation of* p-*Dichlorobenzene and* 1 : 3 : 5-*Trichlorobenzene. Partial Rate Factors for Chlorobenzene.*

By D. R. Augood, D. H. Hey, and Gareth H. Williams.

The proportions of the three isomeric chlorodiphenyls formed in the phenylation of chlorobenzene by means of both benzoyl peroxide and the Gomberg reaction have been determined. Together with the results reported in Part II,* these provide a direct assessment of the partial rate factors for the phenylation process. The three nuclear positions are activated slightly towards attack by phenyl radicals, the sequence of the partial rate factors being $o > p > m$. A brief comparison of these results with theoretical predictions is made. Competitive experiments have been carried out on the action of phenyl radicals derived from benzoyl peroxide on mixtures of *p*-dichlorobenzene and of *s*-trichlorobenzene with nitrobenzene, and the relative rates of phenylation of the polysubstituted benzenes so obtained are compared with values for the same quantities calculated from the partial rate factors for chlorobenzene on the assumption that the substituents contribute additively and independently to the energy of activation for substitution at any one position.

In Part II * was reported the determination by direct and indirect methods of the rate of attack by phenyl radicals on chlorobenzene relatively to that on benzene. This quantity, ${}^{\mathrm{PhCl}}_{\mathrm{PhH}}K$, enables a complete specification to be made of the influence of the substituent chlorine atom on the homolytic substitution reaction in terms of the partial rate factors for the *o*-, *m*-, and *p*-positions, provided that the ratio of isomerides formed in the phenylation of chlorobenzene is known. Analytical methods based on the isolation of the individual isomerides are fundamentally unsuitable for use in the determination of the composition of the mixture of isomerides, since the large differences in solubility prevent assessment of the amounts present. In particular, in comparing the results of the present determinations with those of previous preparative experiments (Grieve and Hey, *J.*, 1934, 1797; Hey, *ibid.*, p. 1966; Butterworth, Heilbron, Hey, and Wilkinson, *J.*, 1938, 1386; France, Heilbron, and Hey, *ibid.*, p. 1364; Heilbron, Hey, and Wilkinson, *J.*, 1938, p. 113; Hey and Waters, *J.*, 1948, 882), it is apparent that the loss of the 2- and the 3-isomeride is much more serious than that of the 4-isomeride, and the orienting influence of the chlorine atom given by such experiments is liable to serious distortion (cf. Waters, *J.*, 1948, 727). Hence, in the present determination, no attempt has been made to isolate the individual isomerides from the mixture obtained in the phenylation reaction, but, rather, the mixture has been analysed by comparison of its infra-red spectrum with the spectra of the three pure isomerides, which were prepared independently. The proportions so obtained are very much more reliable than any obtained previously, and the accuracy of the determination is of the order of $\pm 2\%$.

It has been shown (Bradfield and Jones, *Trans. Faraday Soc.*, 1941, **37**, 726; Bird and Ingold, *J.*, 1938, 918), for heterolytic (electrophilic) substitution, that the effect of substituents is concerned mainly with the energy of activation for substitution at the various positions in the nucleus, and that the frequency factor is substantially independent of the nature of the directing substituent. The same conditions are probably fulfilled in homolytic aromatic substitution, and such an assumption is implicit in theoretical treatments of organic reactivity towards free radicals (cf. Brown, *J.*, 1950, 691, 2730, 3249; 1951, 1612, 1950).

If the partial rate factors for *o*-, *m*-, and *p*-substitution in a monosubstituted benzene derivative PhX are F_o, F_m, and F_p, respectively, then, provided the two substituents contribute additively and independently to the activation energy for substitution at any

* Part II, *J.*, 1952, 2094.

given position, the relative rate of substitution in the disubstituted compound p-$C_6H_4X_2$ is given by

$$^{p\text{-}C_6H_4X_2}_{PhH}K = \tfrac{1}{6}(4F_oF_m) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

since in this compound four equivalent positions are available for substitution, each of which is *ortho* with respect to one substituent X, and *meta* with respect to the other. In the compound $1:3:5$-$C_6H_3X_3$ there are three equivalent positions available for substitution, each of which is *ortho* with respect to two of the substituents X, and *para* with respect to the third. The relative rate of substitution in this compound is therefore given by

$$^{s\text{-}C_6H_3X_3}_{PhH}K = \tfrac{1}{6}(3F_o^2F_p) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Thus, comparison of the measured values of the above two quantities K with the values obtained from equations (1) and (2) by substitution of the measured values of F_o, F_m, and F_p for chlorobenzene affords a check on the assumption of the additivity of substituent effects, on the basis of which these relations are derived.

Experimental methods and results

Preparation of Mixtures of Isomeric Chlorodiphenyls.—(i) *Gomberg reaction.* Redistilled aniline (15·5 g.; 1/6 mole) was dissolved in a warmed mixture of water (13 ml.) and hydrochloric acid (35 ml.). When cooled, the resulting suspension of the hydrochloride was diazotised at 5° with sodium nitrite (13 g.) in water (24 ml.). Chlorobenzene (200 ml.) was added to the diazotised solution, and the mixture was stirred vigorously while 5N-sodium hydroxide (*ca.* 40 ml.) was added dropwise, and then for a further 10 hours. In experiment (*a*) the mixture was acidified; much tar separated, and the organic material was extracted with benzene. In experiment (*b*) the organic layer was separated directly from the aqueous alkali. After being dried ($CaCl_2$), the solutions were distilled, and the products collected as orange-coloured oils, b. p.s (*a*) 82—120°/0·1 mm., (*b*) 82—160°/0·1 mm. These distillations, and all subsequent distillations mentioned in this paper, were carried out with great care, the apparatus and techniques described in Part II (*loc. cit.*) being used. The yields obtained are given in Table 1. Product (*a*) was redistilled. Product (*b*) was dissolved in benzene, and when light petroleum (b. p. 60—80°) was added to the solution a small quantity of flocculent material was precipitated. This was redissolved by gentle warming, and the solution was passed through a short alumina column, and eluted with benzene–light petroleum (b. p. 60—80°). The mixture of isomerides was obtained by distillation of the eluate, a little involatile resin remaining. Both products were divided into two portions, one of which was repeatedly washed in light petroleum solution with small quantities of concentrated sulphuric acid to remove the orange colour. The solutions were then washed with aqueous sodium hydrogen carbonate and water. In each case the spent acid and aqueous washes were extracted with light petroleum (b. p. 60—80°), and the extracts combined with the main petroleum solutions. These were dried (Na_2SO_4) and distilled. The mixtures of isomerides were obtained as colourless oils. Very little material was lost as a result of this treatment (Table 1). From each experiment two mixtures (one orange and the other colourless) were thus obtained for analysis (*a*,1), (*a*,2), (*b*,1), and (*b*,2). Mixtures (*a*,2) and (*b*,2) were those which had been treated with sulphuric acid, and were therefore colourless.

The differences in yields are thought to be due to the different procedures used for the separation of the organic and the aqueous phases in the preparation. Some tar had separated in (*a*) but not in (*b*), owing to the acidification of (*a*), and any coprecipitation of chlorodiphenyls with the tar would reduce the yield of final product.

Table 1.

			H_2SO_4 treatment	
Expt.	Product, g.	Yield, %	Wt. treated, g.	Wt. of product, g.
(*a*)	2·940	15·6	1·847	1·672
(*b*)	6·200	32·8	2·408	2·200

(ii) *Peroxide reaction.* The standardised procedure outlined in Part II (*loc. cit.*) was used for the isolation of the diaryl fraction from the products of reactions (*c*), (*d*), and (*e*). In experiment (*c*), 9 g. of benzoyl peroxide and 300 ml. of chlorobenzene were used, and in experiments (*d*) and (*e*), 6 g. and 200 ml., respectively. A portion of product (*e*) was chromatographed before redistillation; hence two portions (*e*,1) and (*e*,2) were obtained, one of which had

been chromatographed. In each case a high-boiling resin was collected at 0·1 mm. (bath-temp. 200—350°). The combined resin was refluxed for 12 hours with 2·5N-sodium hydroxide in 50% aqueous ethanol. The solution was then extracted with warm benzene after the alcohol had been distilled off. 0·39 G. of benzoic acid was isolated from the aqueous solution and the resin was fractionally distilled out from the dried benzene extract. The resin was a yellow glassy solid, b. p. 194—250°/17 mm., as the main product. This was redistilled, and the middle fraction collected and shown by analysis to consist mainly of chloroterphenyls (Found: C, 82·4; H, 5·2; Cl, 12·8. Calc. for $C_{18}H_{13}Cl$: C, 81·7; H, 4·2; Cl, 13·4%). The formation of resins in this reaction was expected in the light of the experience of their formation gained in the competitive experiments with benzene and chlorobenzene, and with chlorobenzene and pyridine (see Part II, *loc. cit.*). The results are summarised in Table 2.

TABLE 2.

Expt.	Diaryl fraction, g.	Resin, g.	Benzoic acid, g.	$(Ph{\cdot}CO_2)_2$ accounted for, %
(*c*)	3·770	3·783	2·14	88·5
(*d*)	2·366	2·692	1·45	90·2
(*e*)	2·487	2·329	1·44	86·0

Spectrographic Analysis.—For the infra-red spectrographic analysis of the mixtures of 2-, 3-, and 4-chlorodiphenyl a Grubb Parsons instrument was used with an automatic pen recorder. In order to determine the range in which the suitable absorption bands of the chlorodiphenyls lay and so to enable a choice of solvent to be made, the spectra of the three pure isomerides were taken. The 2- and the 4-isomeride were used as crystalline powders in Nujol mulls, and the liquid 3-chlorodiphenyl as a capillary film between rock-salt plates. The 3- and the 4-isomeride possessed characteristic bands in the region 11—15 μ. The corresponding band for the 2-isomeride was very close to a strong band common to all three and, consequently, was of no use for quantitative analysis. Nitromethane, which has no pronounced absorption bands in this region, was used as solvent. Its spectrum was first recorded in a 130-μ cell, the speed of the wave-length scanning and of the slit closing being adjusted so that, as nearly as possible, the energy of transmission recorded was constant over the required range.

The spectra of the solutions under examination were then taken, under strictly reproducible conditions. The "calibration" spectra of the three pure isomerides were obtained by using solutions containing about 0·4 g./10 ml. In order to check the accuracy of the determination, the spectra of three test solutions (*f*), (*g*), and (*h*), containing known amounts of the pure isomerides, were taken, and their compositions calculated from the spectra by the procedure outlined below. The results are given in Table 3.

TABLE 3. *Analysis of mixtures of chlorodiphenyls.*

	Known compositions, %			Compositions calc. from spectra, %		
Solution	2-	3-	4-	2-	3-	4-
(*f*)	39·15	32·15	28·7	42·4	30·6	27·1
(*g*)	44·3	32·5	23·2	48·8	29·5	21·7
(*h*)	0	61·9	38·1	0	62·4	37·6

Finally, the spectra of the experimental mixtures (*a*,1), (*a*,2), (*b*,1), (*b*,2), (*c*), (*d*,1), (*d*,2), (*e*,1), and (*e*,2)* were taken, solutions containing about 1·5 g./10 ml. being used, and the compositions of the mixtures calculated by the procedure outlined below. The results are given

TABLE 4. *Analysis of products obtained in phenylation of chlorobenzene.*

	Composition, %				Composition, %		
Solution	2-	3-	4-	Solution	2-	3-	4-
(*a*,1)	64·5	21·3	14·2	(*d*,1)	61·4	25·0	13·6
(*a*,2)	65·8	20·5	13·7	(*d*,2)	57·6	27·1	15·3
(*b*,1)	63·4	22·7	13·9	(*e*,1)	60·3	25·9	13·8
(*b*,2)	64·5	22·2	13·1	(*e*,2)	59·5	27·0	13·5
(*c*)	62·8	24·6	12·6	Mean	62·2	24·0	13·8

in Table 4. The figure shows the spectra obtained for the three pure isomerides, and one experimental mixture (*a*,2), all corrected for background absorption (including solvent).

Calculation of Ratios of Isomerides.—The Beer–Lambert law, $-\log(I_t/I_i) = kc$, is assumed, where I_t and I_i represent respectively the transmitted and the incident radiation, k is the

* The solutions (*d*,1) and (*d*,2) arise from the fact that two separate analyses were performed on mixture (*d*).

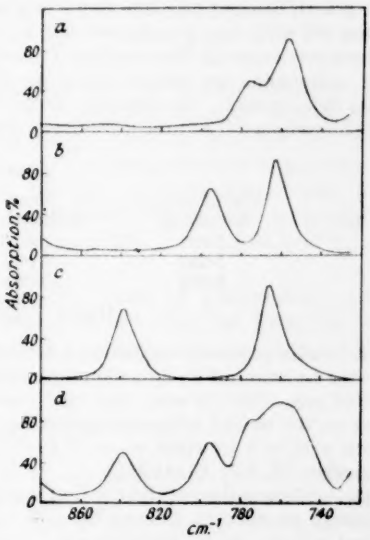
product of the extinction coefficient and the cell thickness, and c is the concentration of the absorbing substance in moles/l. For a mixture of substances x, y, and z at concentration C_x, C_y, and C_z respectively, at a fixed wave-length (in practice the absorption peak of one of the substances x, y, and z),

$$-\log (I_t/I_i) = k_1C_x + k_2C_y + k_3C_z = Y \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Similarly, at another wave-length,

$$-\log (I_t/I_i) = k_4C_x + k_5C_y + k_6C_z = Z \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The quantities Y and Z are obtained by measurement from the spectra of the mixture, and of the solvent, and the six values of k from the spectra of the pure substances at the wave-length



a, 2-*Chlorodiphenyl* (0·4065 *g.*).
b, 3-*Chlorodiphenyl* (0·4005 *g.*).
c, 4-*Chlorodiphenyl* (0·4111 *g.*).
d, *Mixture a*,2 (1·4219 *g.*).

All quantities per 10 *ml. of nitromethane.*
Cell thicknesses, 130 μ.

concerned, by the use of the Beer–Lambert equation, the concentrations in these cases being known. Since the total weight X of the mixture to be analysed is equal to the sum of the weights of the individual isomerides composing the mixture,

$$C_x + C_y + C_z = X \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

By solution of the simultaneous equations (3), (4), and (5) the values of C_x, C_y, and C_z, and hence the composition of the mixture of isomerides, are obtained. The wave-lengths used for obtaining the quantities Y and Z were 795 and 839 cm.$^{-1}$, which are the absorption maxima of the 3- and the 4-isomeride respectively.

Direct Determination of $^{p\text{-}C_6H_4Cl_2}_{PhNO_2}K$.—Benzoyl peroxide (6 g.) was allowed to decompose in an equimolar mixture (200 g.) of nitrobenzene and *p*-dichlorobenzene in a thermostat at 80° for 72 hours. The mixed product was isolated and analysed by estimation of the nitro-compound by titration with titanous chloride. The standard procedure described in Part II (*loc. cit.*) was employed. The results are given in Table 5.

TABLE 5.

Expt. no.	Diaryl fraction, g.	Nitrodiphenyl, %	Forerun, g.	Cl, % in forerun	Correction $Cl_2C_6H_3Ph$, mg.	Corr. wt. of diaryl fraction, g.	Nitrodiphenyl, % (corr.)	$^{p\text{-}C_6H_4Cl_2}_{PhNO_2}K$	$(Ph\text{-}CO_2)_2$ accounted for, %
1	4·287	57·00	0·419	2·39	32	4·319	56·58	0·685	84·7
2	4·418	58·82	0·631	5·11	101	4·519	57·51	0·660	89·9

Hence, $^{p\text{-}C_6H_4Cl_2}_{PhNO_2}K = 0·672$.

After a portion of the product had been used for the analysis, the remainder was warmed with a little light petroleum (b. p. 60—80°), in which the nitrodiphenyls are only sparingly soluble, and the yellow solution decanted from the remaining orange oil. This was repeated twice, and the combined petroleum extracts were washed four times with concentrated sulphuric acid. The spent acid was extracted with light petroleum, and the extracts were all added to the main petroleum solution. This colourless solution was washed with aqueous sodium hydrogen carbonate, and with water, and dried (Na_2SO_4). The solvent was then evaporated, and the remaining oil distilled (b. p. 157°/10 mm.; 112°/1 mm.; 100°/0·3 mm.). The 2 : 5-dichlorodiphenyl was obtained as a colourless oil (n_D^{20} 1·6167) in 37% yield (calc. on weight of benzoyl peroxide) (Found: Cl, 32·1. Calc. for $C_{12}H_8Cl_2$: Cl, 31·8%).

Direct Determination of $^{s\text{-}C_6H_3Cl_3}_{PhNO_2}K$.—Expts. 3 and 4 were carried out with benzoyl peroxide (5 g.) in an equimolar mixture of 1 : 3 : 5-trichlorobenzene (100 g.) and nitrobenzene (56·5 ml.), and Expt. 5 with benzoyl peroxide (5 g.) in a mixture of 1 : 3 : 5-trichlorobenzene (97 g.) and nitrobenzene (70 ml.), *i.e.*, a molar ratio of 1 : 1·2767. The agreement between the results of these experiments confirms the conclusion (Part II, *loc. cit.*) that the proportions in which the competing compounds are present have no effect on the relative rates derived from the competitive experiments. No fore-runs were collected in these experiments, since the b. p.s of 2 : 4 : 6-trichlorodiphenyl and the nitrodiphenyls are very similar. The results are in Table 6.

TABLE 6.

Expt. no.	Wt. of diaryl fraction, g.	Nitrodiphenyl, %	$^{s\text{-}C_6H_3Cl_3}_{PhNO_2}K$	$(Ph\cdot CO_2)_2$ accounted for, %
3	3·427	38·15	1·254	75·1
4	3·337	37·60	1·283	72·9
5	3·521	44·64	1·224	71·1

Hence, $^{s\text{-}C_6H_3Cl_3}_{PhNO_2}K = 1{\cdot}25$.

2 : 4 : 6-*Trichlorodiphenyl* was isolated from the mixed product by the procedure employed above for the isolation of 2 : 5-dichlorodiphenyl. The b. p.s recorded in the final distillation were 172°/15 mm., 163°/10 mm., and 124°/1 mm. The colourless oil, obtained in 42% yield (calculated on the weight of benzoyl peroxide), solidified, and the solid was crystallised from dilute acetic acid to a constant m. p. of 62·5° (Found: C, 55·2; H, 2·8; Cl, 42·2. $C_{12}H_7Cl_3$ requires C, 56·0; H, 2·7; Cl, 41·3%).

Reagents.—Nitromethane (Light & Co.) was boiled under reflux in a stream of dry nitrogen, passed through an alumina column (30 × 3 cm.), dried ($CaCl_2$), and distilled through a 4-ft. helix-packed column (b. p. 101°/760 mm.). *p*-Dichlorobenzene (B.D.H.) was twice distilled through a similar column (b. p. 174°/760 mm.).

The preparation of 1 : 3 : 5-trichlorobenzene recorded in *Org. Synth.* (**7**, 592) was modified. 2 : 4 : 6-Trichloroaniline (175 g.) was dissolved in a warm mixture of 95% ethanol (1780 ml.) and benzene (469 ml.). Sulphuric acid (125 ml.) was added slowly, followed by powdered sodium nitrite (125 g.), added as quickly as possible. The mixture was stirred for 1 hour at room temperature and then boiled under reflux for a further 3 hours. Two such batches were combined at this stage. The mixture was filtered, and the filtrate diluted to *ca.* 12 l. with water and extracted several times with benzene (2500 ml. in all). The residue from the filtration was added to this benzene solution, which was then dried ($CaCl_2$). After removal of the benzene, the residue was distilled *in vacuo*, and the portion of b. p. 97—100°/17 mm. was collected. This was steam-distilled, distilled twice *in vacuo*, and finally crystallised from glacial acetic acid until of constant m. p. (63°); the yield was 260 g. (88·7%).

2-, 3-, and 4-Chlorodiphenyl were prepared by means of the Gomberg reaction from *o*-, *m*-, and *p*-chloroaniline and benzene. The benzene layers, after separation, were washed with water and dried ($CaCl_2$). The solutions were distilled, and the fractions containing the chlorodiphenyls taken up in light petroleum (b. p. 40—60°) and washed repeatedly with concentrated sulphuric acid until the solutions were colourless. After being washed with aqueous sodium hydrogen carbonate and finally with water, the solutions were dried (Na_2SO_4) and distilled. The 2- and the 4-isomeride were recrystallised to constant m. p., and the 3-chlorodiphenyl, which was an oil, was redistilled until its refractive index did not change on redistillation. 2-Chlorodiphenyl was obtained in 13% yield as colourless needles (m. p. 33·5°) from aqueous ethanol. 3-Chlorodiphenyl was a colourless oil (b. p. 152°/11 mm.; n_D^{20} 1·6186) (yield 22%). 4-Chlorodiphenyl was obtained in 28% yield as colourless plates (m. p. 77°) from light petroleum (b. p. 60—80°).

Discussion

Partial Rate Factors for Phenylation.—(i) *Chlorobenzene.* The relative rate of substitution in chlorobenzene, ${}^{\mathrm{PhCl}}_{\mathrm{PhH}}K$, may be obtained from the values of ${}^{\mathrm{PhCl}}_{\mathrm{PhNO_2}}K$ and ${}^{\mathrm{PhNO_2}}_{\mathrm{PhH}}K$, both of which were determined as reported in Part II (*loc. cit.*), since

$$ {}^{\mathrm{PhCl}}_{\mathrm{PhH}}K = {}^{\mathrm{PhCl}}_{\mathrm{PhNO_2}}K \times {}^{\mathrm{PhNO_2}}_{\mathrm{PhH}}K $$

In this way, ${}^{\mathrm{PhCl}}_{\mathrm{PhH}}K$ is found to be equal to 1·44. Using this value, and the mean values obtained by spectrographic analysis for the ratio of isomerides (Table 4), we obtain the following values for the partial rate factors :

$$ {}^{\mathrm{PhCl}}_{\mathrm{PhH}}F_o = 2{\cdot}7\,; \; {}^{\mathrm{PhCl}}_{\mathrm{PhH}}F_m = 1{\cdot}03\,; \; {}^{\mathrm{PhCl}}_{\mathrm{PhH}}F_p = 1{\cdot}2 $$

Thus, the *o*-position is activated to the greatest extent, the *p*-position slightly, and the *m*-position hardly at all. The ***amounts*** of the isomerides formed vary in the order $o > m > p$. This is an entirely unexpected result since, as pointed out on p. **44**, preparative experiments had led to the isolation of the three isomerides in amounts varying in the order $p > o > (m)$. These partial rate factors may be compared with the corresponding quantities for heterolytic substitution (nitration), which were measured by Bird and Ingold (*J.*, 1938, 918). For that reaction $F_o = 0{\cdot}030$, $F_m = 0{\cdot}000$, and $F_p = 0{\cdot}139$; ${}^{\mathrm{PhCl}}_{\mathrm{PhH}}K$ was then equal to 0·0332.

(ii) p-*Dichlorobenzene and* s-*trichlorobenzene.* The rates of phenylation relative to benzene of *p*-dichlorobenzene and *s*-trichlorobenzene are obtained from the values of ${}^{p\text{-}\mathrm{C_6H_4Cl_2}}_{\mathrm{PhNO_2}}K$ and ${}^{s\text{-}\mathrm{C_6H_3Cl_3}}_{\mathrm{PhNO_2}}K$ (pp. **47**, **48**, respectively) by multiplication by **4**, since ${}^{\mathrm{PhNO_2}}_{\mathrm{PhH}}K$ is equal to 4 (Part II, *loc. cit.*). Thus, we obtain

$$ {}^{p\text{-}\mathrm{C_6H_4Cl_2}}_{\mathrm{PhH}}K = 2{\cdot}7 \quad \text{and} \quad {}^{s\text{-}\mathrm{C_6H_3Cl_3}}_{\mathrm{PhH}}K = 5{\cdot}0 $$

Hence, the partial rate factors for substitution at any position in *p*-dichlorobenzene and *s*-trichlorobenzene are 4·05 and 10·0, respectively. The values of the relative rates predicted from the effect of one chlorine atom on the three nuclear positions, which are obtained by substitution of F_o, F_m, and F_p in equations (1) and (2), are

$$ {}^{p\text{-}\mathrm{C_6H_4Cl_2}}_{\mathrm{PhH}}K = 1{\cdot}8 \quad \text{and} \quad {}^{s\text{-}\mathrm{C_6H_3Cl_3}}_{\mathrm{PhH}}K = 4{\cdot}4 $$

These are of the correct order of magnitude, showing that the assumption made on p. **44** with regard to the additivity of the effects of the substitution is true, at least as a first approximation.

Comparison with Theoretical Predictions.—Two of the quantities which have been used in the theoretical treatment of substitution reactions, namely, free valences (cf. Coulson, *Trans. Faraday Soc.*, 1946, **42**, 265) and atom localisation energies (cf. Wheland, *J. Amer. Chem. Soc.*, 1942, **69**, 900) are relevant to a discussion of homolytic reactivity. Both may be calculated by the molecular-orbital method, provided certain parameters are known or assumed. These parameters are the electronegativity of the hetero-atom, in this case chlorine, from which its Coulomb integral α_{Cl} may be estimated, and the resonance integral $\beta_{\mathrm{C-Cl}}$ of the C–Cl bond. In addition, " auxiliary inductive parameters " are sometimes included in order to allow for the changes in the Coulomb integrals of $\mathrm{C_{(1)}}$, $\mathrm{C_{(2)}}$, and $\mathrm{C_{(6)}}$ of the aromatic nucleus brought about by the inductive effect of the hetero-atom. Both the atom localisation energies and the free valences have been calculated for chlorobenzene, and it is of interest to compare the theoretical predictions with the experimental results.

Partial rate factors may be calculated from atom localisation energies by means of equation (6) :

$$ \log F = (A_r^\circ - A_r)/2{\cdot}303\boldsymbol{R}T \quad . \; . \; . \;

where A_r is the atom localisation energy for homolytic substitution at the position to which F refers, and A_r° is the corresponding localisation energy at any position in benzene. By using the localisation energies calculated by Wheland (*loc. cit.*) and the currently accepted value of −34 kcal. for the standard bond integral, the following values are obtained for the partial rate factors for chlorobenzene :

$$F_o = 4{\cdot}48\,;\ F_m = 1{\cdot}32\,;\ F_p = 1{\cdot}75$$

These values lead to the relative rate ${}^{\mathrm{PhCl}}_{\mathrm{PhH}}K = 2{\cdot}22$. The agreement with experiment is surprisingly good, especially when it is remembered that the partial rate factors depend exponentially on the small energy-difference $A_r^\circ - A_r$. It should be remembered also that the parameters used were chosen so as to predict correctly the observed phenomena of heterolytic substitution and the resonance moment of the compound. Wheland's calculations were also performed at a time when no quantitative data on homolytic reactivity were available. That the order of magnitude of these partial rate factors, in addition to the order of reactivity of the nuclear positions ($o > p > m$), are thus correctly predicted is regarded as a notable achievement.

Partial rate factors are related to free valences by the relation (7) (cf. Brown, *Quart. Reviews*, 1952, **6**, 63),

$$\log F_r = 2x\beta(f_r - f_b)/2{\cdot}303\boldsymbol{R}T \quad . \ . \ . \ . \ . \ . \ . \quad (7)$$

where F_r is the partial rate factor of the rth position of the molecule, f_r is the free valence of that position, f_b is the free valence of any position in benzene, and $x\beta$ is the change in the resonance integrals β_{rm}, $\beta_{rn}\cdots$ brought about by the reagent. Since $x\beta$ is not known, partial rate factors cannot be calculated directly from free valences. The necessary free valences, which are obtained from the bond-orders calculated by Sandorfy (*Bull. Soc. chim.*, 1949, **16**, 615) are as follows :

$$f_o = 0{\cdot}410\,;\ f_m = 0{\cdot}400\,;\ f_p = 0{\cdot}404\,;\ f_b = 0{\cdot}398$$

Once again, it is seen that the order of reactivity ($o > p > m$) is correctly predicted, though the absolute magnitudes of the partial rate factors to which these calculations lead must remain unknown in the absence of knowledge of the changes in the resonance integrals β_{rm}, $\beta_{rn}\cdots$ which accompany the reaction.

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8. *The Synthesis of Trypanocides. Part I. Some Pyrimidylaminoquinoline Derivatives.*

By P. A. BARRETT, (the late) F. H. S. CURD, and W. HEPWORTH.

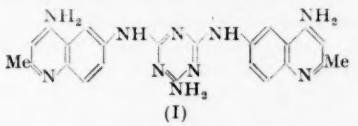
A series of compounds in which pyrimidine derivatives are linked to a quinoline nucleus through a 6-amino-group in the latter are described. The derivatives used included 2-amino-4-chloro-6-methyl-, 4-amino-2-chloro-6-methyl-, and 2 : 6-diamino-4-chloro-pyrimidine; and 6-amino- and 6-amino-2-methyl- and 4 : 6-diamino-2-methyl-quinolines. Quaternary salts obtained by the action of methyl iodide on the pyrimidylaminoquinolines were identical with those obtained by condensation of the corresponding quaternary 6-amino-1-methylquinolinium salts with the chloropyrimidines listed above.

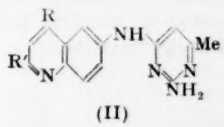
IN this series of papers we report the chemical aspects of an investigation directed towards the discovery of new trypanocides. The chemotherapeutic aspects will be described elsewhere in collaboration with Dr. D. G. Davey.

At the start of our investigation there appeared to be three main outstanding problems in the chemotherapy of trypanosomiasis: the discovery of a satisfactory drug for the treatment of human sleeping sickness in its late stages when the central nervous system has become involved, the therapy of S. American trypanosomiasis (Chagas disease) which is caused by *Trypanosoma cruzi*, and the treatment of *T. congolense* infections in cattle. Of these, the last appeared to be the most important since no completely satisfactory drug has been discovered, although considerable progress has recently been made by the introduction of the phenanthridine derivatives Phenidium Chloride and Dimidium Bromide.

Before the introduction of the above phenanthridine compounds, some experiments had been reported with a compound named Surfen C (I) (for references see Bureau of Hygiene and Tropical Diseases, Review Monograph No. 1, 1946: "A survey of recent work on trypanosomiasis and tsetse flies," p. 39). According to Jensch (*Angew. Chem.*, 1937, **50**, 891), this was discovered during a systematic investigation of derivatives of 4-amino-quinoline. He emphasised the importance of the 4-amino-group and noted the similarity of the tautomeric system in this type of compound to that found in several chemotherapeutically active 5-amino-acridines.

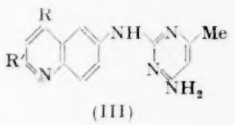
In our researches, which commenced with compounds of types (II and III; R = NH_2, R′ = Me), we sought to simplify the molecule of Surfen C by eliminating the triazine residue which appeared merely to act as a linking group between the two quinoline residues, and to replace one of these by an aminopyrimidine system exhibiting similar tautomeric possibilities.


(I)


(II)

4-Amino-6-(2-amino-6-methyl-4-pyrimidylamino)-2-methylquinoline (II; R = NH_2, R′ = Me) was synthesised by condensation of 4 : 6-diamino-2-methylquinoline (IV; R = NH_2, R′ = H) with 2-amino-4-chloro-6-methylpyrimidine in boiling aqueous solution in presence of hydrochloric acid. In order to prove that condensation had taken place at the 6- and not at the 4-amino-group of the 4 : 6-diamino-2-methylquinoline, 2-amino-4-chloro-6-methylpyrimidine was condensed with 6-amino-4-hydroxy-2-methylquinoline (prepared by hydrolysis of the 6-acetamido-derivative) to give 6-(2-amino-6-methyl-4-pyrimidylamino)-4-hydroxy-2-methylquinoline (II; R = OH, R′ = Me) which was converted by phosphoryl chloride into the 4-chloro-compound (II; R = Cl, R′ = Me) and thence by ammonia in phenol into (II; R = NH_2, R′ = Me), identical with the product made by the first method. Analogously, condensation of 4-amino-2-chloro-6-methylpyrimidine with 4 : 6-diamino-2-methylquinoline gave (III; R = NH_2, R′ = Me).

The preparation of 4 : 6-diamino-2-methylquinoline by the action of ammonia in phenol on 6-acetamido-4-chloro-2-methylquinoline (IV; R = Cl, R′ = Ac) followed by hydrolysis of the resulting 4-amino-compound (IV; R = NH_2, R′ = Ac) was described in B.P. 414,105, and this method has been used for the present work. The synthesis of (IV; R = Cl, R′ = Ac) was not described in detail in the patent and for the present work we have used Kermack and Weatherhead's procedure (*J.*, 1939, 563).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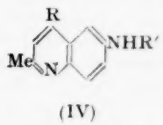
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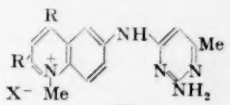
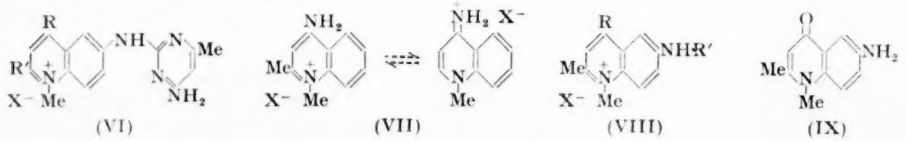

(V)

Since (II; R = NH_2, R′ = Me) and (III; R = NH_2, R′ = Me) possessed only slight trypanocidal activity, attention was directed to the corresponding quaternary salt derivatives (V and VI; R = NH_2, R′ = Me). In these substances the tautomeric possibilities of the 4-amino-2-methylquinoline system are lost, but ionic resonance is still

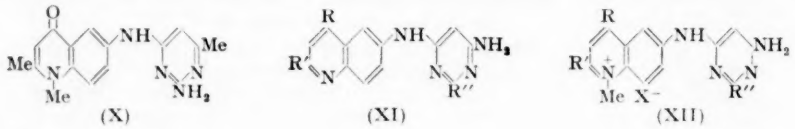
theoretically possible (as in VII), and resonance is of greater importance for biological activity than prototropy (Curd, Landquist, and Rose, *J.*, 1947, **154**; Curd, Davis, Hoggarth, and Rose, *ibid.*, p. 783). Moreover, conversion of a heterocyclic nitrogen atom in an inactive or a slightly active structure into the quaternary state can lead to marked trypanocidal activity (cf. Browning, Morgan, Robb, and Walls, *J. Path. Bact.*, 1938, **46**, 203).

4-Amino-6-(2-amino-6-methyl-4-pyrimidylamino)-1 : 2-dimethylquinolinium iodide (V; R = NH_2, R′ = Me, X = I) and the isomeric iodide (VI; R = NH_2, R′ = Me, X = I) were first prepared by the action of boiling alcoholic methyl iodide on (II and III; R = NH_2, R′ = Me) respectively. That quaternisation had occurred on the quinoline nitrogen atom was proved by the synthesis of (V; R = NH_2, R′ = Me, X = I) from 4 : 6-diamino-1 : 2-dimethylquinolinium chloride (VIII; R = NH_2, R′ = H, X = Cl) and 2-amino-4-chloro-6-methylpyrimidine, and of (VI; R = NH_2, R′ = Me, X = I) in a similar manner, 4-amino-2-chloro- being used in place of 2-amino-4-chloro-6-methylpyrimidine. The proof depended, however, on confirmation of the structure of (VIII; R = NH_2, R′ = H, X = Cl). This compound was synthesised by treatment of 6-acetamido-4-amino-2-methylquinoline with methyl sulphate in nitrobenzene at 100°, followed by hydrolysis of the resulting methosulphate (VIII; R = NH_2, R′ = Ac, X = SO_4Me) with boiling hydrochloric acid. That it does in fact possess the structure assigned to it was proved by its hydrolysis with N-sodium hydroxide to a compound possessing the *N*-methylquinolone structure: 6-amino-1 : 2-dimethylquinol-4-one (IX). Boiling 2N-sodium hydroxide similarly hydrolyses (V; R = NH_2, R′ = Me, X = I) to (X), which was also prepared by reaction between 6-amino-1 : 2-dimethylquinol-4-one and 2-amino-4-chloro-6-methylpyrimidine.



The investigation was then extended to the preparation of (XII; R = NH_2, R′ = R″ = Me, X = I) and (XII; R = R″ = NH_2, R′ = Me, X = I). The former was made by two methods: condensation of 4 : 6-diamino-2-methylquinoline with 6-amino-4-chloro-2-methylpyrimidine to give (XI; R = NH_2, R′ = R″ = Me), followed by quaternisation with methyl iodide in boiling alcohol; and by condensation of 4 : 6-diamino-1 : 2-dimethylquinolinium chloride with 6-amino-4-chloro-2-methylpyrimidine followed by conversion into the iodide. The second compound resulted from the reaction of (VIII; R = NH_2, R′ = H, X = Cl) with 4-chloro-2 : 6-diaminopyrimidine in acetic acid at 150—160°. 4-Amino-6-(2 : 6-diamino-4-pyrimidylamino)-2-methylquinoline was obtained by reaction of 4 : 6-diamino-2-methylquinoline with 2 : 6-diamino-4-chloropyrimidine.

Concurrently, and for comparative purposes, we prepared by similar methods a number of analogous substances lacking the 4-amino-group in the quinoline nucleus; these included 6-(2-amino-6-methyl-4-pyrimidylamino)-1 : 2-dimethylquinolinium chloride (V; R = H, R′ = Me, X = Cl), the iodide (VI; R = H, R′ = Me, X = I) of its isomer, the



corresponding quinoline derivatives (V and VI; R = R′ = H, X = I), and 6-(6-amino-2-methyl-4-pyrimidylamino)- (XII; R = R′ = H, R″ = Me, X = I) and 6-(2 : 6-diamino-4-pyrimidylamino)-1-methylquinolinium iodide (XII; R = R′ = H, R″ = NH_2, X = I).

The 6-aminoquinoline and 6-amino-2-methylquinoline quaternary salts used were

prepared from 6-acetamido-quinoline and -2-methylquinoline by methyl sulphate in nitrobenzene, followed by hydrochloric acid. 6-Amino-1 : 2-dimethylquinolinium iodide was obtained by essentially this method by Browning, Cohen, Ellingworth, and Gulbransen (*Proc. Roy. Soc.*, 1926, *B*, **100**, 293) but neither this nor the corresponding chloride was adequately characterised. Attempts to prepare 6-amino-1-methylquinolinium iodide by Claus and Schnell's method (*J. pr. Chem.*, 1896, **53**, 119), by reaction of 6-aminoquinoline and methyl iodide under pressure, or by reaction in benzene or *via* the methosulphate gave unsatisfactory products.

Experimental

6-*Acetamido*-4-*amino*-1 : 2-*dimethylquinolinium Salts* (VIII; R = NH_2, R′ = Ac, X = Hal).—6-Acetamido-4-amino-2-methylquinoline (4·5 g.) was dissolved in nitrobenzene (40 c.c.) at 100° and methyl sulphate (2·8 g.) added during 5 minutes with stirring, which was continued at this temperature for 1 hour. The precipitated methosulphate was collected, after cooling, washed free from nitrobenzene with acetone, and dried. It was then dissolved in the minimum quantity of water, treated with carbon and filtered, and the filtrate saturated with sodium chloride. The precipitated *chloride* crystallised from 95% alcohol in colourless needles (yield, 59%), m. p. 318° (Found: C, 55·2; H, 6·5; N, 14·5; Cl′, 12·8. $C_{13}H_{16}ON_3Cl,H_2O$ requires C, 55·0; H, 6·3; N, 14·8; Cl′, 12·5%). It was converted into the corresponding *iodide* by dissolving it in water and adding potassium iodide. This salt crystallised from 50% aqueous alcohol as colourless needles, m. p. 294—295°, with softening from 285° (Found: C, 42·1; H, 4·7; N, 11·4; I′, 33·8. $C_{13}H_{16}ON_3I,H_2O$ requires C, 41·6; H, 4·8; N, 11·2; I′, 33·9%).

4 : 6-*Diamino*-1 : 2-*dimethylquinolinium Chloride* (VIII; R = NH_2, R′ = H, X = Cl).—The above methosulphate (4·4 g.) was dissolved in 20% hydrochloric acid (15 c.c.), and the solution boiled for 10 minutes and then cooled. The solid which separated was collected, washed with acetone, and crystallised from 20% hydrochloric acid to give the *hydrochloride* of (VIII; R = NH_2, R′ = H, X = Cl) as almost colourless prisms, m. p. 292—293° (Found: C, 51·0; H, 5·85; N, 16·25; Cl, 27·4. $C_{11}H_{14}N_3Cl,HCl$ requires C, 50·8; H, 5·8; N, 16·2; Cl, 27·3%). An aqueous solution of the above hydrochloride was made alkaline to Brilliant-yellow with sodium carbonate, and a little sodium chloride added to give the *chloride* (VIII; R = NH_2, R′ = H, X = Cl), which crystallised from 95% alcohol as yellow laminæ, m. p. 300—301° (Found: C, 55·0; H, 6·4; N, 17·6; Cl′, 15·0. $C_{11}H_{14}N_3Cl,H_2O$ requires C, 54·7; H, 6·6; N, 17·4; Cl′, 14·7%).

6-(2-*Amino*-6-*methyl*-4-*pyrimidylamino*)-4-*hydroxy*-2-*methylquinoline* (II; R = OH, R′ = Me).—6-Amino-4-hydroxy-2-methylquinoline dihydrochloride (6·45 g.), 2-amino-4-chloro-6-methylpyrimidine (4·6 g.) (Gabriel and Colman, *Ber.*, 1899, **32**, 2924), and water (20 c.c.) were refluxed together for 6 hours. The resulting cooled solution was made alkaline with ammonia, and the precipitated product filtered off, washed with water, and dried (yield, 7·8 g.). Crystallised from aqueous 2-ethoxyethanol, the *compound* (II; R = OH, R′ = Me) formed very pale yellow needles, m. p. 356—357° (decomp.) (Found: C, 56·45; H, 6·1; N, 22·2. $C_{15}H_{15}ON_5,2H_2O$ requires C, 56·75; H, 6·0; N, 22·1%).

6-(2-*Amino*-6-*methyl*-4-*pyrimidylamino*)-4-*chloro*-2-*methylquinoline* (II; R = Cl, R′ = Me).—The preceding compound (10 g.) and phosphoryl chloride (20 c.c.) were mixed. When the resulting vigorous reaction had subsided the mixture was refluxed for 20 minutes, then cooled and poured into dilute sodium hydroxide (250 c.c.). The resulting product was collected, washed alkali-free with water, and crystallised from dry methanol to give the *chloro*-compound (6·3 g.) as almost colourless needles, m. p. 254° (Found: C, 60·0; H, 5·0; N, 23·3. $C_{15}H_{14}N_5Cl$ requires C, 60·3; H, 4·7; N, 23·4%).

4-*Amino*-6-(2-*amino*-6-*methyl*-4-*pyrimidylamino*)-2-*methylquinoline* (II; R = NH_2, R′ = Me).—(*a*) 4 : 6-Diamino-2-methylquinoline (13·2 g.), 2-amino-4-chloro-6-methylpyrimidine (10·8 g.), water (150 c.c.), and 36% hydrochloric acid (18 c.c.) were refluxed together for 1 hour, and the reaction mixture cooled and made just alkaline with ammonia. On addition of a little sodium chloride, the *hydrochloride* rapidly separated and was filtered off and crystallised from 50% aqueous alcohol; colourless fine needles, m. p. 345° (decomp.) (Found: C, 55·9; H, 5·5; N, 26·0; Cl, 10·8. $C_{15}H_{16}N_6,HCl,0·5H_2O$ requires C, 55·3; H, 5·5; N, 25·8; Cl, 10·9%). The *base*, obtained by treating a solution of the hydrochloride with sodium hydroxide, crystallised from 60% alcohol as colourless needles, m. p. 299—300° (Found: C, 60·1; H, 6·0; N, 28·2. $C_{15}H_{16}N_6,H_2O$ requires C, 60·4; H, 6·0; N, 28·2%). The base formed different hydrates of the same m. p. When the monohydrate was boiled with a little absolute alcohol

it dissolved but denser *anhydrous* base was deposited immediately; m. p. 302—303° (Found : C, 64·0; H, 5·8; N, 30·0. $C_{15}H_{16}N_6$ requires C, 64·3; H, 5·7; N, 30·0%).

(*b*) 6-(2-Amino-6-methyl-4-pyrimidylamino)-4-chloro-2-methylquinoline (4·3 g.) was dissolved in phenol (8 g.), the solution heated to 100°, and ammonia passed in briskly. The temperature rose to 120° and then began to fall. At this stage, with continued passage of ammonia, the temperature was raised to, and kept at 180° for 3 hours. The mixture was then cooled somewhat and poured into dilute sodium hydroxide. The resulting precipitate was collected, washed alkali-free with water, and crystallised from 50% aqueous alcohol (Found: C, 58·3; H, 6·5; N, 27·1. $C_{15}H_{16}N_6,1{\cdot}5H_2O$ requires C, 58·6; H, 6·2; N, 27·3%) to give, after dehydration as above, the same material as in (*a*), m. p. and mixed m. p. 299—300°.

4-*Amino*-6-(2-*amino*-6-*methyl*-4-*pyrimidylamino*)-1 : 2-*dimethylquinolinium Salts* (V; R = NH_2, R′ = Me, X = Hal).—(*a*) 4-Amino-6-(2-amino-6-methyl-4-pyrimidylamino)-2-methylquinoline (8 g.), methyl iodide (14 c.c.), and alcohol (100 c.c.) were refluxed together on the steam-bath for 6 hours. The mixture was cooled and filtered, and the residue crystallised from 50% aqueous alcohol to constant m. p. (at least three crystallisations were usually required) to give the *iodide* (V; R = NH_2, R′ = Me, X = I) as very pale yellow fine needles, m. p. 322—323° (Found : C, 42·5; H, 4·9; N, 18·3; I′, 28·3. $C_{16}H_{19}N_6I,2H_2O$ requires C, 41·9; H, 5·0; N, 18·3; I′, 27·7%).

(*b*) A mixture of 4 : 6-diamino-1 : 2-dimethylquinolinium chloride (5·6 g.), 2-amino-4-chloro-6-methylpyrimidine (3·6 g.), water (50 c.c.), and 36% hydrochloric acid (6 c.c.) was heated to boiling. Solution occurred, followed almost immediately by separation of colourless material. The reaction was completed on the steam-bath (1 hour), the mixture then cooled and filtered and the product crystallised from alcohol–water (3 : 1) to give needles of the *hydrochloride* of the chloride (V; R = NH_2, R′ = Me, X = Cl), m. p. 351—352° (Found: C, 50·2; H, 5·7; N, 21·8; Cl′, 18·7. $C_{16}H_{19}N_6Cl,HCl,H_2O$ requires C, 49·9; H, 5·7; N, 21·8; Cl′, 18·4%). With aqueous sodium iodide it gave the corresponding *iodide hydrochloride* (or *chloride hydriodide*), very pale yellow needles, m. p. 316—317° (from 50% aqueous alcohol) (Found : C, 40·4; H, 4·3; N, 17·3; I, 26·5. $C_{16}H_{19}N_6I,HCl,H_2O$ requires C, 40·4; H, 4·6; N, 17·6; I, 26·6%). Re-treatment of this salt with hot aqueous sodium iodide gave the *iodide hydriodide*, yellowish needles (from water), m. p. 323—324° (Found : C, 34·7; H, 3·9; N, 15·4; I, 44·9. $C_{16}H_{19}N_6I,HI,0{\cdot}5H_2O$ requires C, 34·4; H, 3·8; N, 15·0; I, 45·4%). When the chloride hydrochloride was suspended in hot water at 80°, and sodium carbonate added to faint alkalinity (Brilliant-yellow), it passed transiently into solution and the corresponding *chloride* (V; R = NH_2, R′ = Me, X = Cl) separated; it crystallised from 50% aqueous alcohol as colourless fine needles, m. p. 336—338° (Found : C, 53·9; H, 6·1; N, 22·9; Cl, 10·1. $C_{16}H_{19}N_6Cl,1{\cdot}5H_2O$ requires C, 53·7; H, 6·2; N, 23·5; Cl, 9·9%). A solution of this chloride in water, treated with potassium iodide, gave the iodide as a *monohydrate* but otherwise identical with that obtained in (*a*), m. p. and mixed m. p. 322—323° (Found : C, 43·1; H, 5·1; N, 18·3; I′, 29·0. $C_{16}H_{19}N_6I,H_2O$ requires C, 43·6; H, 4·8; N, 19·1; I′, 28·9%).

6-*Amino*-1 : 2-*dimethylquinol*-4-*one* (IX).—4 : 6-Diamino-1 : 2-methylquinolinium chloride hydrochloride (5 g.) and N-sodium hydroxide (50 c.c.) were boiled together under reflux until evolution of ammonia had ceased (3 hours). The mixture was cooled, and the yellow material which separated was the *quinolone*, yellow prisms, m. p. 321—323° (from water) (Found : C, 70·1; H, 6·4; N, 14·4. $C_{11}H_{12}ON_2$ requires C, 70·05; H, 6·4; N, 14·85%). The same chloride hydrochloride was unchanged by 36% hydrochloric acid at 170—180° (14 hours) or in refluxing aqueous solution at pH 11 (15 minutes).

6-(2-*Amino*-6-*methyl*-4-*pyrimidylamino*)-1 : 2-*dimethylquinol*-4-*one* (X).—(*a*) 6-Amino-1 : 2-dimethylquinol-4-one (0·9 g.), 2-amino-4-chloro-6-methylpyrimidine (0·6 g.), 36% hydrochloric acid (1 c.c.), and water (10 c.c.) were refluxed together for 1 hour, and the solution cooled and made alkaline to Clayton-yellow with sodium hydroxide. The precipitated product was the *quinolone* (X), fine yellow needles (from 50% aqueous alcohol), m. p. 365° (decomp.) (Found : C, 64·5; H, 5·5; N, 23·7. $C_{16}H_{17}ON_5$ requires C, 65·0; H, 5·75; N, 23·7%).

(*b*) 4-Amino-6-(2-amino-6-methyl-4-pyrimidylamino)-1 : 2-dimethylquinolinium iodide (2 g.) and N-sodium hydroxide (50 c.c.) were refluxed together till evolution of ammonia ceased (3 hours). The cooled reaction mixture was filtered, and the solid crystallised from 50% alcohol to give the same material as in (*a*), m. p. and mixed m. p. 365° (decomp.) (Found : N, 24·0%).

4-*Amino*-6-(4-*amino*-6-*methyl*-2-*pyrimidylamino*)-2-*methylquinoline* (III; R = NH_2, R′ = Me).—4 : 6-Diamino-2-methylquinoline (4·2 g.), 4-amino-2-chloro-6-methylpyrimidine (3·4 g.) (Gabriel and Colman, *loc. cit.*), water (50 c.c.), and 36% hydrochloric acid (6 c.c.) were boiled together under reflux for 4 hours. After cooling, the colourless crystalline *dihydrochloride* which

had separated was washed with acetone and gave needles (5 g.), m. p. >300° (previous loss of water), from 50% aqueous alcohol (Found, in material dried at 100°: C, 47·75; H, 5·7; N, 21·9; Cl, 18·5. $C_{15}H_{16}N_6,2HCl,1·5H_2O$ requires C, 47·3; H, 5·5; N, 22·1; Cl, 18·7%). The *base*, obtained by addition of sodium hydroxide to a solution of the hydrochloride in water, crystallised from alcohol as very pale yellow prisms, m. p. 272—273° (Found: C, 56·8; H, 6·3; N, 26·4. $C_{15}H_{16}N_6,2H_2O$ requires C, 57·0; H, 6·3; N, 26·6%).

4-*Amino*-6-(4-*amino*-6-*methyl*-2-*pyrimidylamino*)-1 : 2-*dimethylquinolinium Salts* (VI; R = NH_2, R′ = Me).—(*a*) The above base (3 g.), methyl iodide (7 c.c.), and alcohol (50 c.c.) were refluxed together for 6 hours. After cooling, the product was collected, washed with acetone, dried, and crystallised from 50% aqueous alcohol containing a few drops of ammonia. The *iodide* formed pale yellow needles (2·3 g.), m. p. 340° (decomp.) with previous softening (Found: C, 45·5; H, 4·5; N, 19·8; I, 30·2. $C_{16}H_{19}N_6I$ requires C, 45·6; H, 4·5; N, 19·9; I, 30·2%).

(*b*) 4-Amino-2-chloro-6-methylpyrimidine (3·6 g.), 4 : 6-diamino-1 : 2-dimethylquinolinium chloride (5·6 g.), water (50 c.c.), and 36% hydrochloric acid (6 c.c.) were heated together at 100° for 1 hour. The product which separated was collected, after cooling, washed with acetone, and crystallised from 75% aqueous alcohol to give the *hydrochloride* of the chloride (VI; R = NH_2, R′ = Me, X = Cl) (7·5 g.) as fine colourless needles, m. p. 366° (decomp.) (Found: C, 48·0; H, 6·0; N, 21·0; Cl, 17·0. $C_{16}H_{19}N_6Cl,HCl,2H_2O$ requires C, 47·7; H, 6·0; N, 20·8; Cl, 17·6%). When treated in hot water with sodium carbonate to alkalinity to Brilliant-yellow, this salt gave the *chloride* (VI; R = NH_2, R′ = Me, X = Cl), which separated from 50% aqueous alcohol as yellow prisms, m. p. >380° (Found: C, 58·0; H, 5·6; N, 25·0; Cl, 10·5. $C_{16}H_{19}N_6Cl$ requires C, 58·2; H, 5·75; N, 25·4; Cl, 10·75%). The corresponding iodide, after crystallisation from 50% aqueous alcohol, was identical with that made by method (*a*), m. p. and mixed m. p. 340° (decomp.) (Found: C, 45·3; H, 4·5; N, 19·9; I, 30·2%).

4-*Amino*-6-(4-*amino*-2-*methyl*-6-*pyrimidylamino*)-2-*methylquinoline* (XI; R = NH_2, R′ = R″ = Me).—4 : 6-Diamino-2-methylquinoline (3·5 g.), 6-amino-4-chloro-2-methylpyrimidine (2·9 g.) (Baddiley, Lythgoe, McNeil, and Todd, *J.*, 1943, 383), water (50 c.c.), and 10N-hydrochloric acid (2·2 c.c.) were boiled together under reflux for 4 hours. After cooling, the product was collected and crystallised from 50% aqueous alcohol to give the *dihydrochloride* as pale yellow needles, m. p. >380° (Found: C, 42·8; H, 6·2; N, 19·9; Cl′, 16·9, 17·0. $C_{15}H_{16}N_6,2HCl,3·5H_2O$ requires C, 43·1; H, 6·0; N, 20·2; Cl′, 17·1%). The corresponding *base*, obtained by rendering a solution of the hydrochloride alkaline to Clayton-yellow, crystallised from 50% aqueous alcohol as fine colourless needles, m. p. 292—294° (Found: C, 62·9; H, 5·9; N, 29·0. $C_{15}H_{16}N_6,0·5H_2O$ requires C, 62·3; H, 5·9; N, 29·0%).

4-*Amino*-6-(4-*amino*-2-*methyl*-6-*pyrimidylamino*)-1 : 2-*dimethylquinolinium Salts* (XII; R = NH_2, R′ = R″ = Me).—(*a*) The preceding compound (6 g.), methyl iodide (10 c.c.), and alcohol (100 c.c.) were refluxed on the steam-bath overnight. Rapid dissolution occurred, followed shortly by deposition of the *iodide*. After cooling, this was collected; it crystallised from 50% aqueous alcohol as yellow needles, m. p. 344° (decomp.) (Found: C, 43·8; H, 5·0; N, 18·7; I, 28·6. $C_{16}H_{19}N_6I,H_2O$ requires C, 43·7; H, 4·8; N, 19·1; I, 28·9%). In another experiment it was obtained as the *dihydrate* (Found: C, 42·5; H, 4·8; N, 18·6; I′, 27·6. $C_{16}H_{19}N_6I,2H_2O$ requires C, 41·9; H, 5·0; N, 18·3; I′, 27·7%).

(*b*) 4 : 6-Diamino-1 : 2-dimethylquinolinium chloride hydrochloride (5·6 g.), 6-amino-4-chloro-2-methylpyrimidine (3·6 g.), and water (50 c.c.) were boiled under reflux for 2 hours. The product which separated on cooling was collected and dissolved in boiling water, and the solution made alkaline to Brilliant-yellow with sodium carbonate and salted out with sodium chloride. The precipitated *chloride* (XII; R = NH_2, R′ = R″ = Me, X = Cl) crystallised from 50% aqueous alcohol as colourless fine needles which became yellow at 100°, and had m. p. 358° (decomp.) (Found, in air-dried material: C, 54·8; H, 6·0; N, 23·8; Cl, 10·6. $C_{16}H_{19}N_6Cl,H_2O$ requires C, 55·1; H, 6·0; N, 24·1; Cl, 10·2%). It was converted into the corresponding *iodide* by the usual method; m. p. 344° (decomp.) undepressed on admixture with material made by method (*a*) (Found: C, 43·0, 43·1; H, 4·6; N, 18·7; I, 28·1. $C_{16}H_{19}N_6I,1·5H_2O$ requires C, 43·0; H, 4·9; N, 18·7; I, 28·3%).

4-*Amino*-6-(2 : 6-*diamino*-4-*pyrimidylamino*)-2-*methylquinoline* (XI; R = R″ = NH_2, R′ = Me).—4 : 6-Diamino-2-methylquinoline hydrochloride (10·2 g.), 2 : 6-diamino-4-chloropyrimidine (6·7 g.) (Hull, Lovell, Openshaw, and Todd, *J.*, 1947, 41), and acetic acid (9 c.c.) were heated together at 150—160° for 16 hours. The mixture rapidly became fluid and thereafter gradually solidified. The cooled mixture was dissolved in hot water, and the solution treated with carbon, filtered, and made alkaline with sodium hydroxide. The product, initially precipitated as an oil, rapidly solidified and was then collected, washed with water, and boiled with a little 50%

alcohol. The insoluble material (9·4 g.), m. p. 335—336° (decomp.), crystallised from propanol to give the *product* as a buff-coloured powder of unchanged m. p. (Found: C, 59·5; H, 5·4; N, 34·2. $C_{14}H_{15}N_7$ requires C, 59·8; H, 5·35; N, 34·9%).

4-*Amino*-6-(2 : 6-*diamino*-4-*pyrimidylamino*)-1 : 2-*dimethylquinolinium Iodide* (XII; R = R″ = NH_2, R′ = Me, X = I).—4 : 6-Diamino-1 : 2-dimethylquinolinium chloride hydrochloide (4 g.), 2 : 6-diamino-4-chloropyrimidine (2·2 g.), and acetic acid (3·1 c.c.) were stirred and heated together at 150—160° for 2 hours, the original fluid melt then having solidified. The cooled reaction mixture was dissolved in hot water, sodium carbonate added to make the solution alkaline to litmus, and excess of sodium iodide added. The precipitated *iodide* was filtered off when cold, and crystallised from 50% aqueous alcohol (XII; R = R″ = NH_2, R′ = Me, X = I) as a colourless powder (2·65 g.), m. p. 314° (decomp.) (Found: C, 41·4; H, 4·4; N, 22·7; I, 28·7. $C_{15}H_{18}N_7I,0·5H_2O$ requires C, 41·7; H, 4·4; N, 22·7; I, 29·4%).

6-*Amino*-1 : 2-*dimethylquinolinium Chloride*.—A suspension of 6-acetamido-2-methylquinoline (30·4 g.) (Hamer, *J.*, 1921, **119**, 1436) in nitrobenzene (150 c.c.) was heated on the steam-bath till dissolved; methyl sulphate (16 c.c.) was added, and heating continued for ½ hour. Rapid separation of colourless crystalline material took place. The solid was filtered from the cooled mixture, washed with acetone, and dried. A solution of this product in 20% hydrochloric acid (160 c.c.) was boiled for 15 minutes and cooled. The precipitate was washed with acetone, and crystallised from 20% hydrochloric acid to give 6-*amino*-1 : 2-*dimethylquinolinium chloride hydrochloride* as pale buff needles, m. p. 267° (decomp.) (Found: C, 49·8; H, 6·25; N, 10·2; Cl, 26·2. $C_{11}H_{13}N_2Cl,HCl,H_2O$ requires C, 50·2; H, 6·1; N, 10·6; Cl, 27·0%). A solution of this hydrochloride in water was made alkaline with sodium carbonate, and sodium chloride added. The precipitated 6-*amino*-1 : 2-*dimethylquinolinium chloride* crystallised from 95% ethanol as brownish-yellow needles, m. p. 282—283° (Found: C, 58·4; H, 6·65; N, 12·55; Cl, 15·8. $C_{11}H_{13}N_2Cl$ requires C, 58·3; H, 6·6; N, 12·4; Cl, 15·7%).

6-(2-*Amino*-6-*methyl*-4-*pyrimidylamino*)-1 : 2-*dimethylquinolinium Chloride* (V; R = H, R′ = Me, X = Cl).—6-Amino-1 : 2-dimethylquinolinium chloride (4·2 g.), 2-amino-4-chloro-6-methylpyrimidine (2·8 g.), water (25 c.c.), and 36% hydrochloric acid (3 c.c.) were refluxed together for 1 hour. The solution was made alkaline with sodium hydrogen carbonate and cooled. The *chloride* which separated crystallised from 50% aqueous alcohol in yellow needles, m. p. 304—305° (Found: C, 53·3; H, 6·6; N, 19·3; Cl, 10·2. $C_{16}H_{18}N_5Cl$ requires C, 53·3; H, 6·4; N, 19·4; Cl, 9·8%).

6-(4-*Amino*-6-*methyl*-2-*pyrimidylamino*)-1 : 2-*dimethylquinolinium Iodide* (VI; R = H, R′ = Me, X = I).—6-Amino-1 : 2-dimethylquinolinium chloride hydrochloride (5 g.), 4-amino-2-chloro-6-methylpyrimidine (2·8 g.), water (25 c.c.), and 36% hydrochloric acid (1 c.c.) were boiled together under reflux for 1 hour. The reaction mixture was made alkaline to Brilliant-yellow with sodium carbonate, and potassium iodide added. The precipitated *iodide* crystallised from 50% aqueous alcohol in yellow needles, m. p. 246—248° (Found: C, 45·5, 45·6; H, 4·8, 4·7; N, 16·7. $C_{16}H_{18}N_5I,H_2O$ requires C, 45·2; H, 4·7; N, 16·5%).

6-(2-*Amino*-6-*methyl*-4-*pyrimidylamino*)*quinoline* (II; R = R′ = H).—2-Amino-4-chloro-6-methylpyrimidine (7·2 g.) and 6-aminoquinoline hydrochloride (9 g.) in water (50 c.c.) and 36% hydrochloric acid (1 c.c.) were similarly condensed. The resulting clear solution was treated with carbon, filtered, and made alkaline with ammonia. The precipitated oily *product* quickly solidified and crystallised from alcohol as yellowish needles, m. p. 233—234° (Found: C, 64·7; H, 5·6; N, 26·8. $C_{14}H_{13}N_5,0·5H_2O$ requires C, 64·6; H, 5·4; N, 26·9%).

6-*Acetamido*-1-*methylquinolinium Iodide*.—To 6-acetamidoquinoline (18·6 g.) in nitrobenzene (100 c.c.) at 100° methyl sulphate (15 c.c.) was added during 5 minutes with stirring, which was continued for 3 hours. The mixture was cooled, and the almost colourless quaternary methosulphate was collected, washed with acetone, and dried. It was dissolved in a small volume of cold water, the solution treated with carbon and filtered, and excess of potassium iodide added. The precipitated *iodide* crystallised from water as yellow tablets, decomp. >280° (Found: C, 43·9; H, 3·9; N, 8·8; I, 38·9. $C_{12}H_{13}ON_2I$ requires C, 43·9; H, 3·95; N, 8·55; I, 38·8%).

6-*Amino*-1-*methylquinolinium Salts*.—The crude methosulphate prepared as described in the preceding experiment (12 g.), water (10 c.c.), and hydrochloric acid (20 c.c.) were boiled together for 10 minutes. The solution was cooled, and acetone (50 c.c.) was added to precipitate 6-*amino*-1-*methylquinolinium chloride hydrochloride* (6·2 g.), m. p. 246—247° (decomp.). This crystallised from 36% hydrochloric acid–ethanol (1 : 1) as colourless prisms, m. p. 246—247° (decomp.) (Found: C, 52·1; H, 5·1; N, 12·1. $C_{10}H_{11}N_2Cl,HCl$ requires C, 52·0; H, 5·2; N, 12·1%). The hydrochloride (2 g.) was dissolved in water (10 c.c.), and the solution made alkaline with sodium carbonate and divided into two portions. Addition of sodium chloride to

one portion, and recrystallisation of the product from ethanol, gave **6-*amino*-1-*methylquinolinium chloride*** as long yellow prisms, m. p. 244° (Found: C, 56·05; H, 6·15; N, 13·15; Cl, 16·0. $C_{10}H_{11}N_2Cl,H_2O$ requires C, 56·5; H, 6·1; N, 13·2; Cl, 16·7%). The other portion with sodium iodide gave the *iodide* as orange needles, m. p. 194—195°, from ethanol (Found: C, 39·9; H, 4·15; N, 9·55. $C_{10}H_{11}N_2I,H_2O$ requires C, 39·5; H, 4·3; N, 9·2%).

6-(2-*Amino*-6-*methyl*-4-*pyrimidylamino*)-1-*methylquinolinium Salts* (V; R = R′ = H).—(*a*) 6-Amino-1-methylquinolinium chloride (4 g.) and 2-amino-4-chloro-6-methylpyrimidine (2·8 g.) were heated in boiling water (25 c.c.) containing 36% hydrochloride acid (3 c.c.) for 1 hour, and the mixture made alkaline with sodium hydrogen carbonate and cooled. The product which separated was washed with acetone and crystallised from 50% aqueous alcohol to give the *chloride* (V; R = R′ = H, X = Cl) as golden-yellow needles (6·6 g.), m. p. 277—278° (Found: C, 53·5; H, 6·3; N, 20·4. $C_{15}H_{16}N_5Cl,2H_2O$ requires C, 53·35; H, 5·9; N, 20·7%). The corresponding *iodide* (V; R = R′ = H, X = I) crystallised from 50% aqueous alcohol as orange needles, m. p. 258—259° (Found: C, 42·4; H, 4·9; N, 16·7; I, 29·5. $C_{15}H_{16}N_5I,2H_2O$ requires C, 42·0; H, 4·7; N, 16·3; I, 29·6%).

(*b*) 6-(2-Amino-6-methyl-4-pyrimidylamino)quinoline (4 g.) and methyl sulphate (2 g.) were heated together in nitrobenzene (50 c.c.) at 100—110° for 10 minutes; the deep yellow solid formed was then completely soluble in water. After cooling, it was filtered off, washed with acetone, and dried. This methyl methosulphate was dissolved in water, and potassium iodide added. The precipitated methiodide, crystallised from water, had m. p. 256—258° undepressed on admixture with material made by method (*a*).

(*c*) 6-(2-Amino-6-methyl-4-pyrimidylamino)quinoline (2 g.), methyl iodide (1·5 c.c.), and alcohol (20 c.c.) were heated together in a sealed tube for 6 hours at 100°. After cooling, the product which had separated was washed with alcohol and crystallised from water to give **6-(2-*amino*-6-*methyl*-4-*pyrimidylamino*)-1-*methylquinolinium iodide hydriodide*** as orange needles, m. p. 314—315° (decomp.) (Found: C, 32·9; H, 3·8; N, 12·9; I, 45·5. $C_{15}H_{16}N_5I,HI,1·5H_2O$ requires C, 32·9; H, 3·7; N, 12·8; I, 45·4%).

(*d*) 6-(2-Amino-6-methyl-4-pyrimidylamino)quinoline (2·5 g.), methyl iodide (14 c.c.), and alcohol (50 c.c.) were refluxed together on the steam-bath for 18 hours. After about 1 hour deep yellow crystalline material separated, but on further refluxing this was replaced by a voluminous microcrystalline product. After cooling, this was collected and crystallised from water to give the hydriodide of (V; R = R′ = H, X = I), m. p. 315° (decomp.) undepressed on admixture with the product from (*c*) (Found: I, 46·0%). When this salt was dissolved in water and made alkaline with sodium hydrogen carbonate, and the product crystallised from 50% aqueous alcohol, it gave 6-(2-amino-6-methyl-4-pyrimidylamino)-1-methylquinolinium iodide, m. p. 257° undepressed on admixture with material made by method (*a*).

6-(4-*Amino*-6-*methyl*-2-*pyrimidylamino*)*quinoline* (III; R = R′ = H).—(*a*) 6-Aminoquinoline (1·55 g.), 4-amino-2-chloro-6-methylpyrimidine (1·45 g.), and aqueous N-hydrochloric acid (11 c.c.) were boiled under reflux for 3 hours. A thick precipitate of yellow crystalline plates was deposited on cooling. These were washed with water, dried, and crystallised from water; the *dihydrochloride* was obtained as yellow plates (2·05 g.), m. p. >360° (Found: C, 48·9; H, 5·25; N, 20·2; Cl, 20·7. $C_{14}H_{13}N_5,2HCl,H_2O$ requires C, 49·1; H, 5·0; N, 20·5; Cl, 20·7%). Its solution was made alkaline with sodium hydroxide; an oil was precipitated, and on standing it solidified and was crystallised from 50% aqueous alcohol, giving the hydrated *base* as pale green prisms, m. p. 100—103° (Found: C, 62·4; H, 5·6; N, 25·9. $C_{14}H_{13}N_5,H_2O$ requires C, 62·5; H, 5·6; N, 26·0%).

(*b*) 6-(4-Chloro-6-methyl-2-pyrimidylamino)quinoline (5 g.) (Curd *et al.*, *J.*, 1947, 1613) and concentrated ammonia (25 c.c.) were heated in a sealed tube at 175° for 12 hours. The product, which separated, on cooling, initially as an oil, gradually solidified and was then purified as under (*a*) to give the same material, m. p. and mixed m. p. 100—101°.

6-(4-*Amino*-6-*methyl*-2-*pyrimidylamino*)-1-*methylquinolinium Iodide* (VI; R = R′ = H, X = I).—(*a*) 6-Amino-1-methylquinolinium chloride (1·9 g.), 4-amino-2-chloro-6-methylpyrimidine (1·4 g.), water (20 c.c.), and 36% hydrochloric acid (1·5 c.c.) were refluxed for 1 hour. While still warm, the mixture was made alkaline with sodium hydrogen carbonate, and potassium iodide added to precipitate the *iodide* which crystallised from water as yellow needles, m. p. 285—286° (Found: C, 45·65; H, 4·45; N, 17·85; I, 32·5. $C_{15}H_{16}N_5I$ requires C, 45·8; H, 4·1; N, 17·8; I, 32·3%).

(*b*) 6-(4-Amino-6-methyl-2-pyrimidylamino)quinoline (3 g.), alcohol (50 c.c.), and methyl iodide (7 c.c.) were refluxed on the steam-bath for 16 hours. The yellow material which had separated crystallised from water to give the *hydriodide* of the iodide (VI; R = R′ = H, X = I)

as yellow needles, m. p. *ca.* 285° (decomp.) (Found : C, 35·2; H, 3·7; N, 13·5; I, 48·3. $C_{15}H_{16}N_5I,HI$ requires C, 34·6; H, 3·3; N, 13·4; I, 48·8%). A solution of this iodide hydriodide in water was made alkaline with sodium hydrogen carbonate and treated with potassium iodide to give the iodide, which, crystallised from water, had m. p. 285—286° undepressed on admixture with material made by method (*a*).

6-(6-*Amino*-2-*methyl*-4-*pyrimidylamino*)*quinoline* (XI; R = R′ = H, R″ = Me).—6-Aminoquinoline hydrochloride (10 g.) and 4-amino-6-chloro-2-methylpyrimidine (7·2 g.) were intimately mixed by grinding, acetic acid (10 c.c.) was added, and the mixture heated at 150—160° for 3 hours with stirring. The whole became fluid below 100° but gradually solidified later. After cooling, the mass was dissolved in water, and the solution treated with carbon and filtered. Addition of sodium hydroxide to the filtrate precipitated the *base* as an oil. This rapidly solidified and was then washed with water, dried, and crystallised from methanol to give yellow laminæ (12·3 g.), m. p. 229—230° (Found : C, 66·6; H, 5·0; N, 27·8. $C_{14}H_{13}N_5$ requires C, 67·0; H, 5·2; N, 27·8%).

6-(6-*Amino*-2-*methyl*-4-*pyrimidylamino*)-1-*methylquinolinium Iodide* (XII; R = R′ = H, R″ = Me, X = I).—The preceding base (3 g.), methyl iodide (7 c.c.), and alcohol (50 c.c.) were refluxed on the steam-bath for 18 hours. The product, which separated rapidly, was collected hot, washed, and dissolved in water (200 c.c.). Addition of sodium hydrogen carbonate precipitated the *iodide*, which crystallised from water in yellow needles (2 g.), m. p. 291—292° (decomp.) (Found : C, 45·6; H, 4·4; N, 17·7; I′, 31·7. $C_{15}H_{16}N_5I$ requires C, 45·7; H, 4·1; N, 17·8; I′, 32·3%).

6-(2 : 6-*Diamino*-4-*pyrimidylamino*)*quinoline* (XI; R = R′ = H, R″ = NH_2).—6-Aminoquinoline hydrochloride (9 g.) and 2 : 6-diamino-4-chloropyrimidine (7 g.) were condensed together as for the 2-methyl compound above (acetic acid, 5 c.c.; 18 hours' heating at 130—140°), and the product worked up as before, but the base was precipitated by ammonia; the oil rapidly solidified, and after collection, washing, and drying, was crystallised from alcohol (yield, 5·7 g.; m. p. 240—245°). A small quantity was sublimed at 180°/0·1 mm., and the sublimate crystallised from alcohol, giving 6-(2 : 6-*diamino*-4-*pyrimidylamino*)*quinoline* as colourless plates, m. p. 248—249° (Found : C, 61·5; H, 4·75; N, 33·3. $C_{13}H_{12}N_6$ requires C, 61·9; H, 4·75; N, 33·3%).

6-(2 : 6-*Diamino*-4-*pyrimidylamino*)-1-*methylquinolinium Iodide* (XII; R = R′ = H, R″ = NH_2, X = I).—(*a*) 6-Amino-1-methylquinolinium chloride hydrochloride (1 g.) and 2 : 6-diamino-4-chloropyrimidine (0·7 g.) were condensed together as above (acetic acid, 1·0 c.c.; 2 hours' heating at 150—160°). The melt first obtained set to a solid mass, which was dissolved in water. The solution was treated with carbon, filtered, and made alkaline with sodium carbonate, and sodium iodide was added. The precipitate was washed with water and crystallised from water to give the *iodide* (XII; R = R′ = H, R″ = NH_2, X = I) as yellow plates (1·1 g.), m. p. 281° (Found : C, 39·8; H, 4·7; N, 20·1; I, 30·95. $C_{14}H_{15}N_6I,1·5H_2O$ requires C, 39·9; H, 4·3; N, 20·0; I, 30·1%).

(*b*) 6-(2 : 6-Diamino-4-pyrimidylamino)quinoline (3 g.), methyl iodide (7 c.c.), and ethanol (50 c.c.) were refluxed together on the steam-bath for 6 hours. The yellow granular material which had separated was filtered off and dissolved in water, and the solution made faintly alkaline with sodium hydrogen carbonate. The precipitate was collected and recrystallised from water to give a product of m. p. 281°, identical with that under (*a*).

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9. *The Synthesis of Trypanocides. Part II.** 4-*Amino*-6-(2-*amino*-1 : 6-*dimethylpyrimidinium*-4-*amino*)-1 : 2-*dimethylquinolinium* ("*Antrycide*" †) *Salts and Related Compounds.*

By A. D. Ainley, (the late) F. H. S. Curd, W. Hepworth, A. G. Murray, and C. H. Vasey.

Prolonged treatment of 4-amino-6-(2-amino-6-methyl-4-pyrimidylamino)-2-methylquinoline (I) with excess of methyl iodide gave a product of high trypanocidal activity, and careful fractionation of the methochloride showed it to be a mixture containing (II; X = I) and (III; X = Cl).

The diquaternary derivatives of (I) were synthesised by unambiguous routes, involving quaternisation of 2-amino-4-chloro-6-methylpyrimidine, separation and identification of the products, and their condensation with 4 : 6-diamino-1 : 2-dimethylquinolinium salts. Thus 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide (XVII; R = Cl, X = I) gave the dichloride (III; X = Cl) ("Antrycide" chloride). Confirmation that linkage between pyrimidine and quinoline nuclei occurred through the 6-position of the latter was obtained by an alternative synthesis of (III; X = Cl) in which (XVII; R = Cl, X = I) was condensed with 6-amino-4-methoxy-1 : 2-dimethylquinolinium iodide, and the methoxy-group in the product was replaced by amino- by treatment with ammonia.

Conditions are described for the quaternisation of (I) with methyl sulphate to give either (II; X = SO_4Me) or (III; X = SO_4Me) as the main product.

Preparations of 4-amino-6-(2-amino-6-methyl-4-pyrimidylamino)-1 : 2-dimethylquinolinium iodide (II; X = I), made by the action of methyl iodide in boiling alcoholic solution on the non-quaternised compound (I), showed varying trypanocidal activity unless rigorously purified: further, material obtained from the mother-liquors of the purification exhibited high activity, suggesting the presence of varying proportions of a highly active contaminant (see Curd and Davey, *Brit. J. Pharm.*, 1950, **5**, 25). This paper describes the isolation of this impurity, its identification, and synthesis of its active constituent, together with that of related compounds by alternative routes.

The substance (substance B), m. p. 300—301°, first isolated from the mother-liquors from the first crystallisations of (II; X = I), was later found to be the main product when the reaction of methyl iodide was carried out in alcohol in a sealed tube at 100°. It appeared to be an entity, $C_{17}H_{22}N_6I_2$, with one or two molecules of water of crystallisation, formed from two molecules of methyl iodide and one of the base (I), to give a dimethiodide, probably (III; X = I) or (IV; X = I).

In the few recorded descriptions of the preparation of quaternary salts of pyrimidine derivatives carrying only amino- or substituted amino-groups as functional substituents, their orientation had not been established. The behaviour of the model compound 2-amino-4-anilino-6-methylpyrimidine (V) (Banks, *J. Amer. Chem. Soc.*, 1944, **66**, 1131) was therefore studied. In boiling alcohol this gave smoothly a monoquaternary iodide; hydrolysis by concentrated hydrochloric acid at 170—180° then gave aniline and 1 : 6-dimethyluracil (VI), establishing the constitution 2-amino-4-anilino-1 : 6-dimethylpyrimidinium iodide (VII), since the constitution of (VI) was considered to be rigidly proved by Behrend and Hesse (*Annalen*, 1903, **329**, 349). Under milder acid conditions the main product was 4-anilino-1 : 6-dimethylpyrimid-2-one (VIII). Hydrolysis of (VII) with alkali also gave (VIII) accompanied by products of further hydrolysis, aniline and 1 : 6-dimethyluracil. 4-Anilino-6-methyl-2-methylthiopyrimidine (IX), prepared by the action of aniline on 4-chloro-6-methyl-2-methylthiopyrimidine (Wheeler and MacFarland, *Amer. Chem. J.*, 1909, **42**, 431), with methyl iodide in boiling ethanol similarly gave the iodide (X), identified by acid hydrolysis to the above compound (VIII).

* Part I, preceding paper.

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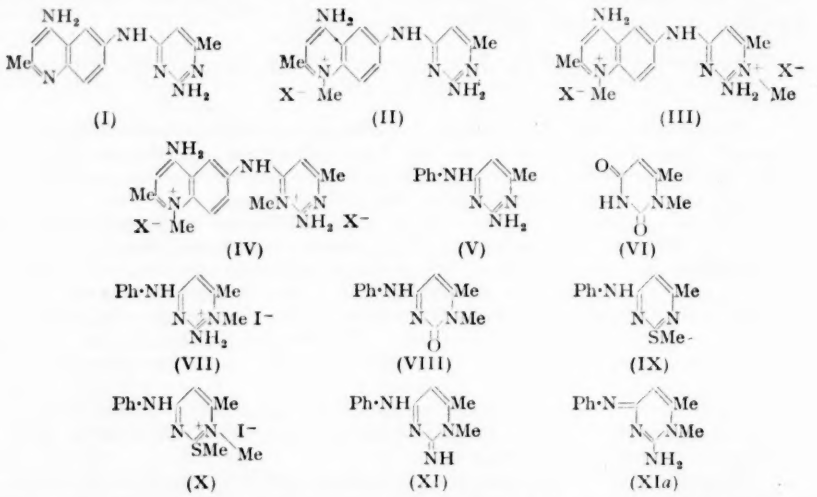
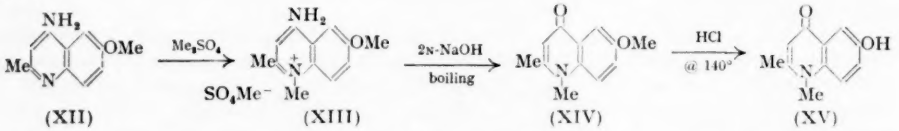
Certain transformations of 2-amino-4-anilino-1 : 6-dimethylpyrimidinium iodide (VII) illustrate the nature of such quaternary salts. With cold alkali, it gave the base (XI or XI*a*), and treatment with hydriodic acid reconstituted the original quaternary salt, thus



indicating that the latter could equally well be regarded as the hydriodide of a dihydroimino-derivative (cf. 2-amino-1-methylquinolinium iodide, Chichibabin *et al.*, *Ber.*, 1921, **54**, 822).

By analogy with the quaternisation of (V) to (VII), the formula (III; X = I) seemed more likely than (IV; X = I) for substance B, and, following the success achieved with the model compound, attempts were made to determine its constitution by acid hydrolysis; despite much effort, no pyrimidine derivative could be isolated. The only product isolated, formed by concentrated hydrochloric acid at 200°, was 6-hydroxy-1 : 2-dimethylquinol-4-one (XV). The structure of this was confirmed by its synthesis from 4-amino-6-methoxy-2-methylquinoline (XII). This was accomplished *via* (XIII) and (XIV) as shown in the scheme. The formation of a 6-hydroxy- from a 6-amino-2-methylquinoline derivative by concentrated hydrochloric acid was further exemplified by the conversion, under similar conditions but at 200°, of 6-amino- into the same 6-hydroxy-1 : 2-dimethylquinol-4-one (XV).



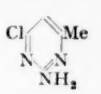
It thus appeared that determination of the constitution of substance B by degradative methods was likely to be difficult, and unambiguous synthetic routes were therefore investigated. This involved a study of the quaternisation of 2-amino-4-chloro-6-methylpyrimidine (XVI), the orientation of the quaternised derivatives, and their subsequent condensation with 4 : 6-diamino-1 : 2-dimethylquinolinium salts, so that linking through the 6-amino-group of the latter was effected.

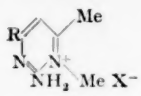
2-Amino-4-chloro-6-methylpyrimidine reacted with methyl iodide, either in a sealed tube at 115° or in solution in 2-ethoxyethanol at 85°. The crude quaternised pyrimidine obtained in both cases was a mixture of two or more compounds. The more soluble and major product, m. p. 261—262° (decomp.), was 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide (XVII; R = Cl, X = I) because with concentrated hydrochloric acid at 160—170° for 12 hours or with boiling 8% sodium hydroxide for 8 hours it gave 1 : 6-

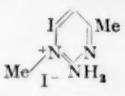
methyluracil (VI), and with aniline in aqueous solution in presence of a little hydrochloric acid it gave 2-amino-4-anilino-1 : 6-dimethylpyrimidinium iodide (VII). The less soluble component, m. p. 260° (decomp.), of the mixture had the empirical formula $C_6H_9N_3I_2$, and it appeared that replacement of chlorine by iodine had taken place with formation of a methiodide of 2-amino-4-iodo-6-methylpyrimidine. It was identified as the 3-methiodide (XVIII) because, on hydrolysis with boiling 2N-sodium hydroxide, 3 : 6-dimethyluracil (XIX) was formed. It condensed with aniline to give an isomer of (VII), which was therefore 2-amino-4-anilino-3 : 6-dimethylpyrimidinium iodide (XX).

From quaternisation of (XVI) in 2-ethoxyethanol at 90—95° there was obtained in addition another apparent entity, m. p. 256° (decomp.), different from (XVIII) but having the same empirical formula. This was at first thought to be 2-amino-4-iodo-1 : 6-dimethylpyrimidinium iodide (XVII; R = X = I) but was later shown to be a mixture of this with (XVIII), since on condensation with aniline a mixture of (VII) and (XX) resulted. Since at a slightly lower temperature (85°) only 2-amino-4-chloro-1 : 6-dimethyl- and 2-amino-4-iodo-3 : 6-dimethyl-pyrimidinium iodide were formed, this would appear to indicate that quaternisation is the first reaction, followed by halogen exchange with methyl iodide, which presumably occurs more readily with 2-amino-4-chloro-3 : 6-dimethylpyrimidinium iodide than with the corresponding 1-methiodide. Such halogen exchanges are similar to that observed, *e.g.*, by Brydówna (*Rocz. Chem.*, 1932, **12**, 89; *Chem. Abs.*, 1933, **27**, 298) who obtained 4-iodo-1-methylquinolinium iodide from 4-chloroquinoline and methyl iodide.

Methyl sulphate similarly reacted with (XVI); in nitrobenzene at 80—90° it gave smoothly the methosulphate (XVII; R = Cl, X = SO_4Me), and addition of sodium iodide to its cold aqueous solution afforded 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide. If, however, the quaternisation was carried out at 100—110° another substance was also formed, which was shown to be anhydro-2-amino-3 : 6-dimethyl-4-sulphatopyrimidinium hydroxide (XXI) by analysis and by acid hydrolysis to the pyrimidone (XXII). This was identical with an authentic sample prepared by methylation of 2-amino-4-hydroxy-6-methylpyrimidine with excess of methyl iodide in alcoholic solution containing 1 equivalent of potassium hydroxide (Jaeger, *Annalen*, 1891, **262**, 369; Ganapathi *et al.*, *Proc. Indian Acad. Sci.*, 1942, **16**, *A*, 115), and proved to have this constitution by its hydrolysis to 3 : 6-dimethyluracil (Majima, *Ber.*, 1908, **41**, 180). Addition of sodium iodide to the aqueous layer after the separation of (XXI) precipitated the iodide (XVII; R = Cl, X = I).


(XVI)


(XVII)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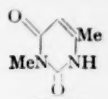
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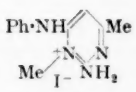
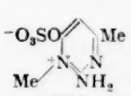
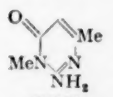
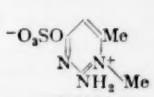

(XX)


(XXI)


(XXII)


(XXIII)

All attempts to isolate 2-amino-4-chloro-3 : 6-dimethylpyrimidinium methosulphate have failed but there is little doubt that it is a precursor of (XXI), and confirmation of its probable formation came from a quaternisation carried out at 80—90° which was worked up by extraction with water, and in which no formation of (XXI) was detected. After precipitation of the 1-methiodide with sodium iodide, the filtrates yielded 2-amino-3 : 6-dimethylpyrimid-4-one.

2-Amino-4-chloro-1 : 6-dimethylpyrimidinium methosulphate underwent an almost quantitative decomposition at 200° into methyl chloride and anhydro-2-amino-1 : 6-dimethyl-4-sulphatopyrimidinium hydroxide (XXIII).

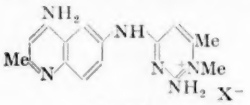
Whereas alkaline hydrolysis of 2-amino-4-chloro-1 : 6-dimethyl- and of 2-amino-4-iodo-3 : 6-dimethyl-pyrimidinium iodide afforded the corresponding dimethyluracils, partial hydrolysis was effected by boiling with water. With the former compound the

solution developed acidity, but if it was buffered at pH 4—6, 2-amino-1 : 6-dimethylpyrimid-4-one semihydriodide gradually separated. Under similar conditions, (XVIII) gave 2-amino-3 : 6-dimethylpyrimid-4-one, though hydrolysis was not so easy.

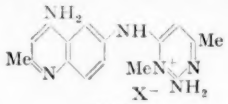
Although the products derived from 2-amino-4-chloro-6-methylpyrimidine and quaternising agents are referred to as quaternary salts, they, like the corresponding 4-anilino-derivatives, can also be regarded as the salts of the corresponding dihydroiminopyrimidines. Rapid hydrolysis has, however, in this case prevented the isolation of the corresponding bases.

When (XVII; R = Cl, X = I) was condensed with 4 : 6-diamino-1 : 2-dimethylquinolinium chloride hydrochloride in boiling water, (III; X = Cl) was obtained. This salt, and the corresponding di-iodide and dibromide, were sparingly soluble in water, whereas the dimethosulphate (III; X = SO_4Me) was very soluble. When the chloride (III; X = Cl) was heated with methyl sulphate in nitrobenzene at 95—100° methyl chloride was evolved and the dimethosulphate remained suspended in the nitrobenzene. 2-Amino-4-chloro-1 : 6-dimethylpyrimidinium iodide was also condensed with 4 : 6-diamino-2-methylquinoline in the presence of hydrochloric acid to give the chloride hydrochloride (XXIV; X = Cl). Proof that the pyrimidinium moiety was linked through the amino-group in the 6-position of the quinoline nucleus was obtained by condensing (XVII; R = Cl, X = I) with 6-amino-4-methoxy-1 : 2-dimethylquinolinium iodide to give 6-(2-amino-1 : 6-dimethylpyrimidinium-4-amino)-4-methoxy-1 : 2-dimethylquinolinium di-iodide which, on treatment with alcoholic ammonia in presence of ammonium chloride at 140°, gave (III; X = I).

The formation of (XVIII) along with (XVII; R = Cl, X = I) in the quaternisation of (XVI) with methyl iodide allowed the preparation of analogous compounds quaternised in the 3-position of the pyrimidine ring. Thus by reaction of (XVIII) with 4 : 6-diamino-1 : 2-dimethylquinolinium chloride hydrochloride, and isolation of the product as the iodide there was obtained the di-iodide (IV; X = I). In contrast to its isomer (III), (IV) was converted into the corresponding base 4-amino-6-(2 : 3-dihydro-2-imino-3 : 6-dimethyl-4-pyrimidylamino)[or 4-amino-6-(2-amino-3 : 4-dihydro-3 : 6-dimethyl-4-pyrimidylimino)]-1 : 2-dimethylquinolinium iodide by sodium carbonate. By condensation with 4 : 6-diamino-2-methylquinoline, (XVIII) gave the hydrochloride of (XXV; X = I).

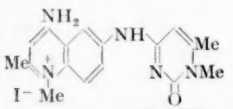


(XXIV)

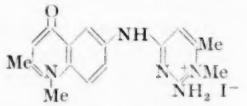


(XXV)

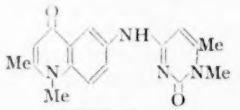
Alkaline hydrolysis of (III) gave two different products according to experimental conditions. Refluxing for 20 minutes with 1 equiv. of sodium hydroxide gave a compound, m. p. 305°, which was considered to be 4-amino-6-(1 : 2-dihydro-2-keto-1 : 6-dimethyl-4-pyrimidylamino)-1 : 2-dimethylquinolinium iodide (XXVI) on account of its non-identity with the isomeric 6-(2-amino-1 : 6-dimethylpyrimidinium-4-amino)-1 : 2-dimethylquinol-4-one iodide (XXVII), m. p. 306°, which was prepared by condensing 6-amino-1 : 2-



(XXVI)



(XXVII)



(XXVIII)

dimethylquinol-4-one with 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide. By an excess of boiling aqueous sodium hydroxide, (III) was converted into (XXVIII), which was also produced by alkaline hydrolysis of (XXVII).

The synthesis by unambiguous routes, and the characterisation, of a number of the possible quaternary derivatives of (I) greatly facilitated the further study of the products of the direct quaternisation reaction. It became clear that substance B and (III; X = I)

were not identical, the former probably being a mixture. When it was converted into the corresponding chloride, and this was treated with sodium carbonate, the resulting mixture was more readily separated, and gave, from aqueous solution, 4-amino-6-(2-amino-1 : 6-dimethylpyridinium-4-amino)-1 : 2-dimethylquinolinium dichloride (III; X = Cl) as the least soluble component. A more soluble product was isolated as the iodide, and identified as (II; X = I).

The quaternisation of (I) with methyl sulphate gave, according to the conditions, either the monoquaternary salt (II; X = SO_4Me) or the diquaternary salt (III; X = SO_4Me).

Experimental

Quaternisation of 4-*Amino*-6-(2-*amino*-6-*methyl*-4-*pyrimidylamino*)-2-*methylquinoline* (I) *with Methyl Iodide.*—(*a*) The base (I) (10 g.), methyl iodide (17·5 c.c.), and alcohol (125 c.c.) were boiled under reflux on the steam-bath for 6 hours. Complete solution was never obtained but the mixture became thick and pink. After cooling, the solid was filtered off, washed with acetone, and dried (13·2 g.); it had m. p. 296—298° (Found: I, 38·0%). This solid (11·2 g.) was crystallised from 50% alcohol, and the mother-liquors (A) retained. The crystalline product (5·4 g.) had m. p. 314—316° (Found: I, 28·5%) and after two further crystallisations from 50% alcohol gave 4-amino-6-(2-amino-6-methyl-4-pyrimidylamino)-1 : 2-dimethylquinolinium iodide (2·8 g.), m. p. 322—323°, as described in Part I (*loc. cit.*).

The mother-liquors (A) were evaporated to dryness to give an orange residue (5·7 g.) (Found: I, 40·1%). This was dissolved in hot water, and the solution made alkaline to Brilliant-yellow with ammonia and salted out with sodium iodide. The precipitated product was collected, washed with acetone, and dried (5·35 g.) (Found: I, 42·0%). This material (4 g.) was crystallised twice from 75% alcohol to give a new *dihydrate* (substance B) (0·45 g.), m. p. 300—301° unchanged on further crystallisation (Found: C, 33·7; H, 4·5; N, 14·2; I, 42·5. $C_{17}H_{22}N_6I_2,2H_2O$ requires C, 34·0; H, 4·5; N, 14·0; I, 42·5%).

(*b*) The base (I) (2·5 g.), methyl iodide (2·5 g.), and alcohol (15 c.c.) were heated together in a sealed tube at 100° for 16 hours. After cooling, the contents of the tube were filtered off and crystallised from 50% alcohol to give the *monohydrate* of substance B, m. p. 300—301° unaltered by further crystallisation and undepressed on admixture with the material described in (*a*) (Found: C, 35·3; 34·8; H, 4·7; 4·4; N, 14·5; 14·4; I, 43·6. $C_{17}H_{22}N_6I_2,H_2O$ requires C, 35·1; H, 4·2; N, 14·45; I, 43·6%).

Separation of the Constituents of Substance B.—Substance B (10 g.) was dissolved in hot water (700 c.c.), and concentrated hydrochloric acid (8·2 c.c.) added. The precipitate, which was filtered off after cooling, still contained iodine, and was therefore freed from iodine by redissolving it in water and salting it out with sodium chloride (yield, 5·9 g.). A sample of this product was reconverted into the di-iodide by treating the aqueous solution with sodium iodide. The above chloride (5·0 g.) was dissolved in water (150 c.c.), and sodium carbonate added until the mixture was alkaline (Brilliant-yellow). The precipitate was collected and extracted with hot water (35 c.c.). The aqueous extract was treated with sodium iodide and cooled, and the product separated. After further recrystallisation from water it had m. p. 326°, undepressed on admixture with 4-amino-6-(2-amino-6-methyl-4-pyrimidylamino)-1 : 2-dimethylquinolinium iodide. The solid residue from the extraction with hot water was purified by repeated crystallisation from a larger volume of hot water to give 4-amino-6-(2-amino-1 : 6-dimethylpyrimidinium-4-amino)-1 : 2-dimethylquinolinium dichloride (III; X = Cl), m. p. 316—317° (decomp.) alone or mixed with an authentic specimen (see p. 67).

2-*Amino*-4-*anilino*-1 : 6-*dimethylpyrimidinium Iodide* (VII).—2-Amino-4-anilino-6-methylpyrimidine (2 g.) (Banks, *loc. cit.*), alcohol (12 c.c.), and methyl iodide (3 c.c.) were refluxed together for 18 hours, the mixture cooled, and the product filtered off. Crystallisation from alcohol gave the *iodide* (VII) as colourless, flat, rectangular prisms (2·6 g.), m. p. 250° (Found: C, 42·5; H, 4·6; N, 16·6; I, 36·9. $C_{12}H_{15}N_4I$ requires C, 42·1; H, 4·4; N, 16·4; I, 37·1%).

When a solution of the above methiodide (2 g.) in warm water (300 c.c.) was cooled and made alkaline to Clayton-yellow with sodium hydroxide, the corresponding *base* (XI or XI*a*) was precipitated. Recrystallised from aqueous alcohol, it formed colourless needles, m. p. 229—230° (Found: C, 67·5; H, 6·5; N, 25·6. $C_{12}H_{14}N_4$ requires C, 67·3; H, 6·5; N, 26·2%). This base was dissolved in dilute hydriodic acid, and the solution made alkaline to Brilliant-yellow with sodium carbonate and treated with sodium iodide, giving the original quaternary salt, m. p. and mixed m. p. 250°.

Acid Hydrolysis of 2-*Amino*-4-*anilino*-1 : 6-*dimethylpyrimidinium Iodide* (VII).—(*a*) The

above methiodide (1 g.) and 9% aqueous hydrochloric acid were heated in a sealed tube at 118—120° for 12 hours. The mixture was filtered, and the filtrate made alkaline with sodium hydroxide. The precipitated product was washed with water and crystallised from aqueous alcohol to give 4-*anilino*-1 : 6-*dimethylpyrimid*-2-*one* (VIII) (0·4 g.) as colourless cubes, m. p. 298—299° (Found : C, 66·8; H, 6·0; N, 19·6. $C_{12}H_{13}ON_3$ requires C, 66·9; H, 6·0; N, 19·5%).

(*b*) The iodide (VII) (1 g.) and concentrated hydrochloric acid (10 c.c.) were heated at 170—180° for 14 hours, diluted with water, and made alkaline with sodium hydroxide. After filtration from a little precipitated material the filtrate was extracted with chloroform, the aqueous layer being retained (A). The chloroform extract was extracted with 3·5% aqueous hydrochloric acid, and the extract treated with sodium nitrite and coupled with alkaline β-naphthol to give benzeneazo-β-naphthol, m. p. and mixed m. p. 131° after crystallisation from alcohol. The aqueous layer (A, above) was acidified with hydrochloric acid and evaporated to dryness. The residue was extracted thoroughly with boiling methanol, the extracts were evaporated to dryness, and the residue was triturated with cold chloroform, dried, and sublimed in a high vacuum at 140—180°. The sublimate was extracted with boiling alcohol (2 c.c.), and the filtered extract allowed to cool. The product which separated crystallised in colourless needles, m. p. 221—222° undepressed on admixture with authentic 1 : 6-dimethyluracil (Found : C, 51·1; H, 5·3; N, 20·0. Calc. for $C_6H_8O_2N_2$: C, 51·4; H, 5·7; N, 20·0%).

Alkaline Hydrolysis of 2-*Amino*-4-*anilino*-1 : 6-*dimethylpyrimidinium Iodide*.—Sodium hydroxide solution (40% ; 30 c.c.) was added to a solution of this iodide (10 g.) in water (30 c.c.), and the resulting suspension was boiled under reflux for 16 hours. Ammonia was evolved, and the originally flocculent precipitate became granular. This crystallised from aqueous ethanol in cubes (2·1 g.), m. p. 298—299°, identical with the pyrimidone (VIII) described above. The alkaline filtrate was extracted with chloroform, and the aqueous solution acidified with hydrochloric acid and evaporated to dryness. The residue was heated to 140—180°/0·3 mm. ; a colourless material sublimed, which crystallised from ethanol in needles, m. p. 221—222°, identical with the 1 : 6-dimethyluracil described above. The chloroform extract was extracted with acid, and the aniline obtained was identified as above (benzeneazo-β-naphthol, m. p. 131°).

4-*Anilino*-6-*methyl*-2-*methylthiopyrimidine* (IX).—Aniline (4 g.), 4-chloro-6-methyl-2-methylthiopyrimidine (7 g.) (Wheeler and MacFarland, *loc. cit.*), and glacial acetic acid (50 c.c.) were heated on the steam-bath with stirring for 45 minutes with concentrated hydrochloric acid (3 drops). The solution was cooled, diluted with water (150 c.c.) and neutralised to Brilliant-yellow with sodium hydroxide. The solid *pyrimidine* (IX) crystallised from a small volume of ethanol in colourless plates (8·5 g.), m. p. 129—131° (Found : C, 62·2; H, 5·55; N, 18·65. $C_{12}H_{13}N_3S$ requires C, 62·2; H, 5·6; N, 18·2%).

4-*Anilino*-1 : 6-*dimethyl*-2-*methylthiopyrimidinium Iodide* (X).—The preceding compound (IX) (5 g.), methyl iodide (7·5 c.c.), and alcohol (30 c.c.) were boiled together under reflux for 12 hours. The *iodide* (X) was filtered off, after cooling, and recrystallised from alcohol as colourless needles, m. p. 240° (decomp.) (Found : C, 42·0; H, 4·7; N, 11·3. $C_{13}H_{16}N_3IS$ requires C, 41·9; H, 4·3; N, 11·3%).

Hydrolysis. The iodide (X) (2 g.) and concentrated hydrochloric acid (30 c.c.) were refluxed together for 6 hours. Methanethiol was evolved. The resulting solution was cooled, filtered, and made alkaline with sodium hydroxide. The precipitated product was washed with water and crystallised from aqueous alcohol to give 4-anilino-1 : 6-dimethylpyrimid-2-one (0·9 g.), m. p. and mixed m. p. 298—299° (Found : C, 67·0; H, 5·9; N, 19·6. Calc. for $C_{12}H_{13}ON_3$: C, 66·9; H, 6·0; N, 19·5%).

Acid Hydrolysis of Substance B.—Substance B (3 g.) was heated with concentrated hydrochloric acid in a sealed tube at 200° for 12 hours. The solid product was separated and crystallised from water to give pale yellow needles of 6-*hydroxy*-1 : 2-*dimethylquinol*-4-*one*, m. p 333° (0·2 g.) (Found : C, 69·35; H, 5·6; N, 7·6. $C_{11}H_{11}O_2N$ requires C, 69·7; H, 5·8; N, 7·4%), identical with that described below.

4-*Amino*-6-*methoxy*-1 : 2-*dimethylquinolinium Methyl Sulphate* (XIII).—4-Amino-6-methoxy-2-methylquinoline (3·5 g.) was dissolved in dry nitrobenzene (40 c.c.) at 90—95°, and methyl sulphate (2·4 g.) added ; the mixture was stirred for 1 hour at 90—95°, cooled, and filtered, and the precipitate was washed with benzene and crystallised from ethanol to give fine colourless needles of the *sulphate* (XIII), m. p. 262—263° (5·4 g.) (Found : C, 49·45; H, 5·7; N, 9·1. $C_{13}H_{18}O_5N_2S$ requires C, 49·6; H, 5·7; N, 8·9%).

6-*Methoxy*-1 : 2-*dimethylquinol*-4-*one*.—To a solution of the foregoing salt (XIII) (4·5 g.) in water (30 c.c.), 8% sodium hydroxide (20 c.c.) was added, and the solution was boiled for 2 hours, ammonia being evolved. After cooling, the precipitate was collected, washed with cold water,

and recrystallised from water to give colourless needles of a hydrated form of **6-*methoxy*-1 : 2-*dimethylquinol*-4-*one*** (XIV), m. p. 84° (2·0 g.), which lost water at 100°, giving the anhydrous compound, m. p. 149—150° (Found, in substance dried *in vacuo* at 80° : C, 70·9; H, 7·1; N, 6·9. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·4; N, 6·9%).

6-*Hydroxy*-1 : 2-*dimethylquinol*-4-*one*.—(*a*) The methoxyquinolone (XIV) (1·2 g.) was heated with concentrated hydrochloric acid in a sealed tube at 140—150° for 12 hours. The product was dissolved in water and made alkaline with ammonia, giving pale yellow needles of the hydroxyquinolone (0·7 g.), m. p. 333° (Found : C, 69·4; H, 6·15; N, 7·15. Calc. for $C_{11}H_{11}O_2N$: C, 69·7; H, 5·8; N, 7·4%).

(*b*) 6-Amino-1 : 2-dimethylquinol-4-one (0·7 g.) (see Part I) was heated with concentrated hydrochloric acid (10 c.c.) at 200° for 12 hours. The dark brown suspension was evaporated to dryness, and the resultant solid was recrystallised from water made alkaline by ammonia, to give pale yellow needles of 6-hydroxy-1 : 2-dimethylquinol-4-one, m. p. 333°, identical with the product described in (*a*).

Quaternisation of **2-*Amino*-4-*chloro*-6-*methylpyrimidine*** (XVI) ***with Methyl Iodide*.**—(*a*) The pyrimidine (XVI) (19·2 g.) and methyl iodide (8·8 c.c.) were heated at 115° ± 3° for 6 hours. The resulting pale cream-coloured solid (34 g.) was finely powdered and extracted with boiling ethyl acetate (200 c.c.), and the insoluble material (26·9 g.) collected. Evaporation of the ethyl acetate extract and crystallisation of the residue gave unchanged (XVI) (6·4 g.), m. p. and mixed m. p. 178—179°. The material insoluble in ethyl acetate was separated by fractional crystallisation from water into two constituents. The more soluble, **2-*amino*-4-*chloro*-1 : 6-*dimethylpyrimidinium iodide*** (XVII; R = Cl, X = I), separated from water as pale cream-coloured plates, m. p. 261—262° (decomp.) (Found : C, 25·2; H, 3·4; N, 14·4%; 1 mg. ≡ 1·332 mg. of Ag halides. $C_6H_9N_3ClI$ requires C, 25·2; H, 3·15; N, 14·7%; 1 mg. ≡ 1·326 mg. of Ag halides). The less soluble constituent, **2-*amino*-4-*iodo*-3 : 6-*dimethylpyrimidinium iodide*** (XVIII), crystallised from water, in which it was sparingly soluble, as small colourless plates, m. p. 260° (decomp.) (Found : C, 19·4; H, 2·4; N, 10·7; I, 67·3. $C_6N_9N_3I_2$ requires C, 19·1; H, 2·4; N, 11·1; I, 67·3%). When the reaction was carried out at a slightly lower temperature (112° ± 3°) for 3 hours, very little quaternisation occurred and 86% of the pyrimidine was recovered unchanged.

(*b*) The pyrimidine (XVI) (50 g.), methyl iodide (24 c.c.), and 2-ethoxyethanol (130 c.c.) were heated in a water-bath at 85° ± 5° for 18 hours; (XVI) gradually dissolved, and pale cream-coloured crystals separated. After cooling, the product was collected and extracted with boiling ethyl acetate (200 c.c.) to remove unchanged material. The insoluble residue (44 g.) was extracted with boiling water (300 c.c.) and filtered hot. The residue crystallised from a large volume of water to give the iodide (XVIII) (4·25 g.), m. p. and mixed m. p. 260° (decomp.). The above hot aqueous extract, on cooling, deposited pale cream-coloured plates (25·4 g.) which crystallised from water to give pure 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide (15·5 g.), m. p. and mixed m. p. 261—262° (decomp.).

Quaternisation of **2-*Amino*-4-*chloro*-6-*methylpyrimidine*** (XVI) ***with Methyl Sulphate*.**—(*a*) A mixture of methyl sulphate (80 c.c.) and nitrobenzene (150 c.c.) was heated to 80—85° with agitation. 2-Amino-4-chloro-6-methylpyrimidine (100 g.) was gradually added (1 hour), the temperature being kept at 80—90°. After a further ½ hour's stirring at this temperature the mixture was cooled and the crystalline product which had separated washed well with acetone (yield, 58%). A small sample was rapidly crystallised from alcohol and dried in a vacuum, to give **2-*amino*-4-*chloro*-1 : 6-*dimethylpyrimidinium methyl sulphate*** (XVII; R = Cl, X = SO_4Me) as pale cream-coloured needles, m. p. 155—157° (decomp.) (Found : C, 31·2; H, 4·5; N, 15·6. $C_7H_{12}O_4N_3ClS$ requires C, 31·15; H, 4·45; N, 15·6%). It is extremely soluble in water. Treatment of an aqueous solution with sodium iodide precipitated the corresponding quaternary iodide, m. p. and mixed m. p. 261—262° (decomp.).

(*b*) After reaction as above, the cooled mixture was treated with water (125 c.c.) and then benzene (125 c.c.), and the aqueous layer was separated and carefully neutralised with sodium hydroxide. Unchanged pyrimidine (9 g.) was precipitated, and filtered off. The filtrate was heated to 70°, and sodium iodide (75 g.) added. On cooling, 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide crystallised, and was washed with alcohol [yield, 53%; m. p. and mixed m. p. 261—262° (decomp.)]. The filtrate was evaporated somewhat under diminished pressure; the solid (24·5 g.) which separated was crystallised from water and identified as 2-amino-3 : 6-dimethylpyrimid-4-one, m. p. 318° undepressed on admixture with material made by the method of Ganapathi *et al.* (*loc. cit.*).

(*c*) After reaction as above, but at 100—110°, water (300 c.c.) and benzene (100 c.c.) were

added, and a white solid separated. This was collected (3 g.), dissolved in dilute sodium carbonate solution, and reprecipitated with hydrochloric acid. Crystallisation from a very large volume of water gave *anhydro*-2-*amino*-3 : 6-*dimethyl*-4-*sulphatopyrimidinium hydroxide* (XXI) as a white powder, m. p. 339—340° (Found: C, 33·0; H, 4·3; N, 19·3; S, 14·4. $C_6H_9O_4N_3S$ requires C, 32·8; H, 4·1; N, 19·15; S, 14·6%), insoluble in all the usual organic solvents. The original aqueous layer was separated from the benzene–nitrobenzene layer and neutralised to pH 7·5 with sodium hydroxide to precipitate unchanged material (13%). This was filtered off, and the filtrate treated with sodium iodide (73 g.) at 70° to give (XVII; R = Cl, X = I) (43%) which, crystallised from water, had m. p. and mixed m. p. 261—263°.

Hydrolysis of (XXI). The anhydro-hydroxide (XXI) (2 g.), water (10 c.c.), and sulphuric acid (7 c.c.) were heated together at 145° for 1½ hours, and the solution cooled and neutralised with sodium hydroxide. It was then evaporated to dryness, and the residue extracted several times with boiling alcohol. The combined extracts deposited a solid on cooling which, recrystallised from alcohol, gave 2-amino-3 : 6-dimethylpyrimid-4-one (XXII), m. p. and mixed m. p. 316—318°.

Anhydro-2-*amino*-1 : 6-*dimethyl*-4-*sulphatopyrimidinium Hydroxide* (XXIII).—The methosulphate (XVII; R = Cl, X = SO_4Me) (50 g.) in a 200-c.c. Kjeldahl flask was plunged into an oil-bath at 200°. The issuing gas was collected in a trap cooled to −79° (solid carbon dioxide–methanol). When gas evolution had ceased (*ca.* 15 min.), the product was cooled to below 100°, and water (150 c.c.) added. Complete solution was momentarily obtained, followed by rapid crystallisation. Recrystallisation of the product from water gave the *anhydro*-compound (XXIII) as colourless crystals (13 g.), m. p. 334—336° (decomp.) (Found: C, 30·6; H, 4·7; N, 17·8. $C_6H_9O_4N_3S,H_2O$ requires C, 30·3; H, 4·65; N, 17·7%), insoluble in the usual organic solvents. The gas evolved during the reaction was identified as methyl chloride (yield, 95%), b. p. −25°.

Hydrolysis of 2-*Amino*-4-*chloro*-1 : 6-*dimethylpyrimidinium Iodide* (XVII; R = Cl, X = I).—(a) *With acid.* The iodide (1 g.) and concentrated hydrochloric acid (10 c.c.) were heated together in a sealed tube at 160° ± 5° for 12 hours, then filtered, and the filtrate was neutralised with sodium hydroxide and evaporated to dryness. The powdered residue was extracted with boiling absolute alcohol (3 × 25 c.c.), and the alcoholic extracts were combined and evaporated to 3 c.c. The crystalline material which separated on cooling recrystallised from alcohol, giving colourless laminæ, m. p. 219—220° undepressed in admixture with authentic 1 : 6-dimethyluracil made by Behrend and Thurn's method (*Annalen*, 1902, **323**, 166).

(b) *With alkali.* The iodide (XVII; R = Cl, X = I) (2·86 g.) and 8% aqueous sodium hydroxide (20 c.c.) were boiled under reflux for 8 hours. Ammonia was evolved. After cooling, the solution was neutralised with hydrochloric acid and evaporated to dryness in a vacuum. The residual solid was finely ground and extracted with boiling absolute alcohol (2 × 25 c.c.), and the combined alcoholic extracts were treated with carbon and evaporated to small bulk. The crystalline 1 : 6-dimethyluracil which separated (0·5 g.), when crystallised from alcohol, had m. p. and mixed m. p. 220°.

(c) *With water.* The iodide (20 g.) and water (100 c.c.) were refluxed together for 5 hours with gradual addition of sodium hydrogen carbonate to keep the solution at pH 4—6. A yellow solid gradually separated. This was collected and purified, first by dissolution in water followed by salting out with sodium iodide, and then by crystallisation from water to give practically colourless crystals of 2-amino-1 : 6-dimethylpyrimid-4-one semihydriodide (see Part III, to be published), m. p. and mixed m. p. 284—285°.

Hydrolysis of 2-*Amino*-4-*iodo*-3 : 6-*dimethylpyrimidinium Iodide* (XVIII).—(a) *With alkali.* The iodide (3·77 g.) and 8% aqueous sodium hydroxide (30 c.c.) were boiled under reflux for 3 hours. Ammonia was slowly evolved. The resulting solution was neutralised with hydrochloric acid, filtered, and evaporated to dryness in a vacuum. Extraction of the residue with boiling alcohol (2 × 30 c.c.), evaporation of the combined extracts to dryness, and crystallisation of the residue from a little water gave long, thin prisms, m. p. 261—262°, undepressed by authentic 3 : 6-dimethyluracil made by Wheeler and McFarland's method (*loc. cit.*).

(b) *With water.* The iodide (1·2 g.) and water (25 c.c.) were boiled under reflux for 4·25 hours. The acidity to Congo-red which developed was neutralised by periodic addition of sodium hydrogen carbonate. After cooling, the mixture was filtered from unchanged material (0·3 g.), m. p. and mixed m. p. 258—259° (decomp.), and made alkaline to Clayton-yellow with sodium hydroxide. The precipitated product was collected and crystallised from water to give 2-amino-3 : 6-dimethylpyrimid-4-one (0·33 g.), m. p. 316—318° undepressed on admixture with authentic material.

Condensation of the Iodide (XVII; R = Cl, X = I) *with Aniline.*—This iodide (5·72 g.) was dissolved in boiling water (50 c.c.), aniline hydrochloride (2·6 g.) added, and the mixture refluxed for 1 hour. The product which separated on cooling was collected and dissolved in water (50 c.c.), and the solution filtered and salted with potassium iodide. The precipitated material crystallised from water to give 2-amino-4-anilino-1 : 6-dimethylpyrimidinium iodide (VII) (5·35 g.), m. p. 250° alone or on admixture with material described above.

4-*Amino*-6-(2-*amino*-1 : 6-*dimethylpyrimidinium*-4-*amino*)-1 : 2-*dimethylquinolinium Salts* (III).—4 : 6-Diamino-1 : 2-dimethylquinolinium chloride hydrochloride (13 g.) and 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide (14·3 g.) were boiled in water (350 c.c.) for ½ hour. The product, which soon began to separate, was collected after cooling, washed with N-hydrochloric acid (50 c.c.), and then with water (50 c.c.), and dissolved in hot water (800 c.c.); the solution (carbon) was filtered, and excess of sodium chloride added to the filtrate. The product so obtained was collected, but as it contained traces of iodide, it was redissolved in hot water (900 c.c.), and a mixture of hydrochloric acid (20 c.c.) and water (30 c.c.) added. The precipitated product was washed acid-free with water and crystallised from water to give the *dichloride* (III; X = Cl) as colourless needles (16·65 g.), m. p. 316—317° (decomp.) (Found: C, 49·2; H, 6·5; N, 19·6; Cl, 16·9. $C_{17}H_{22}N_6Cl_2,2H_2O$ requires C, 48·9; H, 6·2; N, 20·1; Cl, 17·0%). The corresponding "*di-iodide*," prepared by dissolving the above dichloride in hot water and salting it out with excess of sodium iodide, crystallised from water as colourless needles, m. p. 312—313° (decomp.) (Found: C, 33·8; H, 4·0; N, 13·8. $C_{17}H_{22}N_6I_2,2H_2O$ requires C, 34·0; H, 4·3; N, 14·0%). When this quaternary salt was first made it was the *monohydrate*, m. p. 301—302° (decomp.) (Found: C, 34·8; H, 4·3; N, 14·4; I, 43·2. $C_{17}H_{22}N_6I_2,H_2O$ requires C, 35·05; H, 4·1; N, 14·4; I, 43·6%), but subsequently this form could not be obtained either when the compound was made in the above manner or from the quinolinium iodide hydriodide and 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide. The *dibromide* (III; X = Br), prepared from the above dichloride by dissolving it in hot water and adding sodium bromide, crystallised from water as colourless needles, m. p. 316° (decomp.) (Found: C, 41·7, 41·4; H, 5·2, 4·9; N, 17·1, 16·9; Br, 32·4. $C_{17}H_{22}N_6Br_2,H_2O$ requires C, 41·8; H, 4·9; N, 17·2; Br, 32·8%).

Conversion of (III; X = Cl) *into the Corresponding Dimethosulphate.*—The dihydrate of (III; X = Cl) (62 g.) was suspended in nitrobenzene (400 c.c.) and toluene (200 c.c.) and freed from water by azeotropic distillation. Toluene (100 c.c.) was then distilled off, and the mixture cooled to 50°. Methyl sulphate (previously neutralised over potassium carbonate) (41 g.) was added, and the mixture heated at 100° until gas evolution (methyl chloride) was complete (*ca.* 3 hours). After cooling, the product was collected and washed with methanol (100 c.c.). The crude product thus obtained was suspended in methanol (600 c.c.), and the mixture refluxed for 1½ hours, 2N-Sodium carbonate (*ca.* 4 c.c.) was then added gradually to the hot suspension until a sample dissolved in water to give a soluton at pH 6. The suspension was then cooled, and the product collected and dried to give the dimethosulphate (III; X = SO_4Me), m. p. 265—266°, undepressed on admixture with material described on p. 70.

4-*Amino*-6-(2-*amino*-1 : 6-*dimethylpyrimidinium*-4-*amino*)-2-*methylquinoline Salts* (XXIV).—4 : 6-Diamino-2-methylquinoline (2·6 g.) was dissolved in a hot mixture of 2N-hydrochloric acid (22·5 c.c.) and water (7·5 c.c.), a solution of 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide (4·3 g.) in hot water (30 c.c.) added, and the mixture boiled for 1 hour. After cooling, the product was collected and crystallised first from water and then from aqueous 2-ethoxyethanol to give the *hydrochloride* of the iodide (XXIV; X = I) as pale cream-coloured needles, m. p. 260—262° (Found: C, 37·9; H, 5·2; N, 16·4%; 1 mg. ≡ 0·726 mg. Ag halides. $C_{16}H_{19}N_6I,HCl,3H_2O$ requires C, 37·5; H, 5·1; N, 16·4%; 1 mg. ≡ 0·738 mg. Ag halides). The corresponding *hydriodide* was obtained by dissolving this hydrochloride in hot water, making the solution just alkaline with 2N-sodium carbonate, and adding excess of potassium iodide. It separated from water as aggregates of short, cream-coloured needles, m. p. 290—292° (decomp.) (Found, in material dried at 90°: C, 34·0; H, 4·1; N, 14·5. $C_{16}H_{19}N_6I,HI,H_2O$ requires C, 33·8; H, 3·9; N, 14·8%. Found, in material dried at room temperature: C, 32·1; H, 4·4; N, 13·9; I, 41·8. $C_{16}H_{19}N_6I,HI,3H_2O$ requires C, 31·8; H, 4·3; N, 13·9; I, 42·1%). The *hydrochloride* of the chloride (XXIV; X = Cl) was obtained by dissolving the methiodide hydriodide in 2N-hydrochloric acid, and adding 2N-sodium carbonate solution to alkalinity (Brilliant-yellow) and then excess of sodium chloride; cream-coloured needles, m. p. 333° (decomp.) (Found: C, 44·4; H, 5·9; N, 19·6. $C_{16}H_{19}N_6Cl,HCl,3·5H_2O$ requires C, 44·6; H, 6·3; N, 19·5%), were obtained from aqueous alcohol.

6-*Amino*-4-*methoxy*-1 : 2-*dimethylquinolinium Iodide.*—6-Acetamido-4-methoxy-2-methyl-

quinoline (Jacini, *Gazzetta*, 1941, **71**, 53) (47 g.), methyl iodide (28·5 g.), and 2-ethoxyethanol (30 c.c.) were heated under reflux on the steam-bath for 2 hours. After cooling, the thick pasty mass was diluted with ethyl acetate (100 c.c.) and filtered, and the solid well washed with ethyl acetate. Repeated crystallisation from water gave *6-acetamido-4-methoxy-1 : 2-dimethylquinolinium iodide monohydrate* as pale fawn crystals (54 g.), m. p. 313° (Found : N, 7·7. $C_{14}H_{17}O_2N_2I,H_2O$ requires N, 7·2%).

The above product (30 g.) was boiled under reflux with 4N-hydrochloric acid (300 c.c.) for 30 minutes. The solution was then cooled and neutralised to pH 4 by the addition of sodium hydroxide solution. The solid which separated was collected and crystallised from water (2·5 l.) to yield the *iodide* of the 6-amino-compound as yellow needles, m. p. 248° (18 g.) (Found : C, 44·1; H, 4·55; N, 8·4. $C_{12}H_{15}ON_2I$ requires C, 43·65; H, 4·6; N, 8·5%).

6-(2-Amino-1 : 6-dimethylpyrimidinium-4-amino)-4-methoxy-1 : 2-dimethylquinolinium Di-iodide.—The above 6-acetamido-iodide (18·5 g.), the iodide (XVII; R = Cl, X = I) (14·0 g.), concentrated hydriodic acid (15 c.c.), and water (160 c.c.) were boiled under reflux for 1 hour, cooled, and filtered. The solid obtained was crystallised several times from water to give the required di-iodide as a *hemihydrate*, pale yellow crystals, m. p. 305° (22 g.) (Found : C, 37·0; H, 4·35; N, 11·6. $C_{18}H_{23}ON_5I_2,0{\cdot}5H_2O$ requires C, 36·8; H, 4·1; N, 11·9%), sparingly soluble in ethyl alcohol and cold water but readily soluble in boiling water.

Conversion of 4-Methoxy- into 4-Amino-6-(2-amino-1 : 6-dimethylpyrimidinium-4-amino)-1 : 2-dimethylquinolinium Di-iodide.—The methoxy-di-iodide (4·0 g.), 7% ammoniacal ethyl alcohol (25 c.c.), and ammonium chloride (4·0 g.) were heated in a sealed tube at 140° for 6 hours. After cooling, the tube contents were washed out with ethyl alcohol, the excess of ammonia boiled off, and after dilution with water the suspension was neutralised with hydriodic acid. The solid was dissolved in boiling water (300 c.c.), and excess of potassium iodide added. The precipitate was filtered off and crystallised from water, 4-amino-6-(2-amino-1 : 6-dimethylpyrimidinium-4-amino)-1 : 2-dimethylquinolinium di-iodide (3·0 g.) being obtained as pale cream needles, m. p. 310° (decomp.) undepressed on admixture with material prepared as above (Found : C, 34·8; H, 4·4; N, 13·6. Calc. for $C_{17}H_{22}N_6I_2,H_2O$: C, 35·05; H, 4·1; N, 14·4%).

2-Amino-4-anilino-3 : 6-dimethylpyrimidinium Iodide (XX).—Aniline (1·8 c.c.) was added to a suspension of 2-amino-4-iodo-3 : 6-dimethylpyrimidinium iodide (3·77 g.) in water (30 c.c.), and the mixture boiled under reflux for 1 hour. Complete dissolution had not occurred when the product began to separate after a few minutes' boiling. After cooling, the crystalline *iodide* (XX) was collected, washed with a little cold water, and crystallised from water as colourless prisms, m. p. 273° (decomp.) (Found : C, 42·5; H, 4·4; N, 16·1. $C_{12}H_{15}N_4I$ requires C, 42·1; H, 4·4; N, 16·4%). When the above iodide was dissolved in water and treated with excess of 10% sodium carbonate solution, the corresponding base (*2-amino-3 : 4-dihydro-3 : 6-dimethyl-4-phenyliminopyrimidine* or *4-anilino-2 : 3-dihydro-2-imino-3 : 6-dimethylpyrimidine*) was obtained; it crystallised from benzene as colourless rectangular plates, m. p. 220—221° (Found: C, 67·3; H, 6·8; N, 25·8. $C_{12}H_{14}N_4$ requires C, 67·3; H, 6·6; N, 26·2%), or from alcohol as colourless leaflets of the *semi-alcoholate* having the same m. p. (Found : C, 65·4; H, 7·2; N, 23·5. $C_{12}H_{14}N_4,0{\cdot}5C_2H_6O$ requires C, 65·8; H, 7·2; N, 23·6%).

When a suspension of the above base (1·07 g.) in 5N-sodium hydroxide (25 c.c.) was boiled for 1 hour, only a faint trace of ammonia could be detected and the filtrate obtained after cooling, dilution with water (40 c.c.), and collection of the solid, showed a very slight positive test for diazotisable material. The solid recovered (1 g.) was unchanged material, m. p. and mixed m. p. 220—221°.

4-Amino-6-(2-amino-3 : 6-dimethylpyrimidinium-4-amino)-1 : 2-dimethylquinolinium Di-iodide (IV; X = I).—4 : 6-Diamino-1 : 2-dimethylquinolinium chloride hydrochloride (13 g.), 2-amino-4-iodo-3 : 6-dimethylpyrimidinium iodide (18·85 g.) and water (150 c.c.) were refluxed together for 1 hour. The hot mixture was treated with sodium iodide and cooled, and the product (15·8 g.) collected. It was dissolved in hot water (500 c.c.), and the solution made alkaline to Brilliant-yellow with 2N-sodium carbonate (19·5 c.c.) and treated with excess of sodium iodide. The precipitated product, which was very sparingly soluble in water, crystallised from 40% aqueous alcohol to give *4-amino-6-(2-amino-3 : 4-dihydro-3 : 6-dimethyl-4-pyrimidylimino)-1 : 2-dimethylquinolinium iodide* [or the corresponding imino-form] as yellowish prisms, m. p. 328° (decomp.) (Found : C, 46·8; H, 4·8; N, 18·9; I, 29·1. $C_{17}H_{21}N_6I$ requires C, 46·8; H, 4·8; N, 19·3; I, 29·1%). When the above base (2·5 g.) was dissolved in hot 1·3% aqueous hydriodic acid (60 c.c.), and the solution cooled, it gave the *di-iodide* (IV; X = I) which crystallised from water as clusters of pale cream-coloured, long, flat, rectangular prisms, m. p. 295° (decomp.) (Found : C, 36·5; H, 4·4; N, 14·7; I, 44·5. $C_{17}H_{22}N_6I_2$ requires C, 36·2; H,

3·9; N, 14·9; I, 45·0%). The di-iodide (12 g.) was converted into the corresponding *dichloride* by dissolving it in water (500 c.c.) and shaking it with excess of freshly precipitated silver chloride (20 g.) until the solution was free from iodide, followed by evaporation of the filtered solution to dryness under reduced pressure and crystallisation of the residue from 80% propanol (with the addition of a little hydrochloric acid on the first crystallisation); it formed pale cream-coloured tablets, m. p. 247° (decomp.) (Found: C, 48·1; H, 6·3; Cl, 16·7. $C_{17}H_{22}N_6Cl_2,2·5H_2O$ requires C, 47·9; H, 6·3; Cl, 16·7%).

4-*Amino*-6-(2-*amino*-3 : 6-*dimethylpyrimidinium*-4-*amino*)-2-*methylquinoline Iodide* (XXV; X = I).—4 : 6-Diamino-2-methylquinoline dihydrochloride (1·3 g.) was refluxed with 2-amino-4-iodo-3 : 6-dimethylpyrimidinium iodide (1·9 g.) in water (130 c.c.) for 1 hour. The clear solution was cooled, made faintly alkaline with sodium carbonate, and treated with potassium iodide. The sticky precipitate so obtained slowly hardened and was crystallised from water, to give the *hydrochloride* of the iodide (XXV; X = I) as pale cream-coloured prismatic needles, m. p. 245—246° (Found: C, 37·9; H, 4·6; N, 16·7%; 1 mg. ≡ 0·688 mg. of Ag halides. $C_{16}H_{19}N_6I,HCl,2·5H_2O$ requires C, 38·1; H, 5·0; N, 16·7%; 1 mg. ≡ 0·752 mg. of Ag halides).

6-(2-*Amino*-1 : 6-*dimethylpyrimidinium*-4-*amino*)-1 : 2-*dimethylquinol*-4-*one Iodide* (XXVII).—6-Amino-1 : 2-dimethylquinol-4-one (1·95 g.), 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide (3 g.), water (50 c.c.), and concentrated hydrochloric acid (1 c.c.) were refluxed for 1 hour. The resulting solution was treated with excess of sodium iodide and cooled. The product which separated, when crystallised from water and then from 50% alcohol, gave the *iodide* (XXVII) as colourless needles, m. p. 306° (Found: C, 42·4; H, 5·2; N, 14·4; I, 26·0. $C_{17}H_{20}ON_5I,2·5H_2O$ requires C, 42·3; H, 5·2; N, 14·5; I, 26·3%).

6-(1 : 2-*Dihydro*-2-*keto*-1 : 6-*dimethyl*-4-*pyrimidylamino*)-1 : 2-*dimethylquinol*-4-*one* (XXVIII).—(*a*) The di-iodide (III; X = I) (2 g.) and 10% aqueous sodium hydroxide (70 c.c.) were refluxed for 3 hours. The product which had separated was washed with water and crystallised from 50% alcohol to give the *quinolone* (XXVIII) as colourless needles, m. p. >380° (Found: C, 60·7; H, 6·2; N, 16·9. $C_{17}H_{18}O_2N_4,1·5H_2O$ requires C, 60·7; H, 6·2; N, 16·6%).

(*b*) The quinolone iodide (XXVII) (1 g.) was dissolved in boiling water (140 c.c.), 4% sodium hydroxide solution (3 c.c.) added, and the mixture refluxed for 1 hour. The product was collected hot, washed with water, and crystallised from 50% alcohol to give the same compound as in (*a*), m. p. >380° (Found: C, 60·7; H, 5·9; N, 16·8%). Light absorption in 1% hydrochloric acid: Max. 2980 Å, ε 32,920; min. 2650 Å, ε 8764.

4-*Amino*-6-(1 : 2-*dihydro*-2-*keto*-1 : 6-*dimethyl*-4-*pyrimidylamino*)-1 : 2-*dimethylquinolinium Iodide* (XXVI).—The di-iodide (III; X = I) (2 g.) was boiled under reflux with water (50 c.c.) and 4% aqueous sodium hydroxide (4 c.c.) for 20 minutes. The resulting precipitate was collected hot, washed with water, and crystallised from 50% alcohol, giving the *iodide* (XXVI) as practically colourless, short, stumpy needles, m. p. 305° (decomp.) (sintering at 200°) (Found: C, 43·3; H, 5·3; N, 14·5; I, 26·4. $C_{17}H_{20}ON_5I,2H_2O$ requires C, 43·0; H, 5·1; N, 14·8; I, 26·9%). Light absorption in 1% hydrochloric acid: Max. 3020 Å, ε 31,220; min. 2680 Å, ε 8806.

4-*Amino*-6-(2-*amino*-6-*methyl*-4-*pyrimidylamino*)-1 : 2-*dimethylquinolinium Methyl Sulphate* (II; X = SO_4Me).—(*a*) Anhydrous 4-amino-6-(2-amino-6-methyl-4-pyrimidylamino)-2-methylquinoline (I) (11·2 g.) was stirred with 2-ethoxyethanol (160 c.c.) and neutral methyl sulphate (5·3 g.) at room temperature for 4 days. The solid product was filtered off, washed with cold methanol, extracted with hot methanol (100 c.c.), and recrystallised twice from aqueous methanol to give the *methosulphate* (II; X = SO_4Me) as cream-coloured crystals, m. p. 278—279° (4·5 g.) (Found: C, 49·9; H, 5·35; N, 20·4; S, 7·8. $C_{17}H_{22}O_4N_6S$ requires C, 50·2; H, 5·4; N, 20·7; S, 7·9%). This was converted into the corresponding iodide, m. p. 313° (see Part I), by treating an aqueous solution with sodium iodide.

(*b*) The quinoline (I) (11·2 g.) was suspended in nitrobenzene (120 c.c.) and benzene (40 c.c.), and the mixture was freed from traces of water by azeotropic distillation, the benzene being finally distilled off until the temperature of the mixture rose to 145°. It was then cooled to 70°, and methyl sulphate (5·3 g.) was added during ½ hour. The temperature was kept at 70—75° for 18 hours, and the product then filtered off, washed with cold methanol, and recrystallised from aqueous methanol to give the same methosulphate (8·7 g.) as that in (*a*), m. p. and mixed m. p. 278—279°.

Diquaternisation of 4-*Amino*-6-(2-*amino*-6-*methyl*-4-*pyrimidylamino*)-2-*methylquinoline with Methyl Sulphate.*—The quinoline (11·2 g.), suspended in nitrobenzene (120 c.c.) and benzene (40 c.c.), was dried by azeotropic distillation as described above, and methyl sulphate (10·25 g.)

was added at 100—105°. The reaction was slightly exothermic, and the temperature was kept at 120° for 3 hours. The mixture was cooled to 50° and filtered; the residue was washed with cold methanol (100 c.c.), suspended in boiling methyl alcohol (100 c.c.), isolated again by filtration, thoroughly washed with boiling methyl alcohol, and finally crystallised from aqueous methyl alcohol (85% by volume) to give white crystals of 4-amino-6-(2-amino-1 : 6-dimethylpyrimidinium-4-amino)-1 : 2-dimethylquinolinium di(methyl sulphate), m. p. 265—266° (10 g.) (Found: C, 42·6; H, 5·2; N, 16·1; S, 12·3. Calc. for $C_{19}H_{28}O_8N_6S_2$: C, 42·9; H, 5·27; N, 15·8; S, 12·05%).

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10. *The Nature of the Co-ordinate Link. Part VII.* Palladous Complexes of Stable* cis-*Configuration.*

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The *cis–trans* equilibria in benzene solutions of palladous complexes of the type $(MR_3)_2PdCl_2$ (M = P, As, and Sb; R = *n*-alkyl) and of $(SbPh_3)_2PdCl_2$ have been examined by measuring the dielectric constants of their solutions at 25°. The quantities of *cis*-isomers in the solutions of the phosphine and arsine complexes are too small for detection by this method; the solutions of the stibine complexes contain 3·5—40% of the *cis*-isomers in labile equilibrium with their *trans*-isomers, the quantities depending on the group R. The quantities of *cis*-isomers in the equilibria are much smaller than in the analogous platinous series (see Table 1). Only the crystalline *cis*-isomers separate from solutions of $(SbR_3)_2PdCl_2$ because their solubilities are so much smaller than those of their *trans*-isomers. The crystalline complexes $(SbR_3)_2PdCl_2$ provide the first example of a series of palladous complexes which are not chelated yet have stable *cis*-configurations.

The complex chemistry of platinum(II) is very similar to that of palladium(II). Both metals have the same atomic radius, they form only "inner orbital" complexes (Taube, *Chem. Reviews*, 1952, **50**, 69), and their covalently bound ligands occupy a square configuration about the metal atoms. Their complex compounds show much less tendency to dissociate than do those of most bivalent metals, but complexes of palladium are less stable and stereochemically rigid than those of platinum. Thus platinous complexes, L_2PtX_2 (L = neutral ligand, X = univalent acid radical), with few exceptions can be isolated in *cis*- and *trans*-forms but their palladous analogues exist only in one form. *cis*-$(NH_3)_2PdCl_2$ (Grunberg and Shulman, *Compt. rend. Acad. Sci., U.R.S.S.*, 1933, **215**) and *cis*-$(NH_3)_2Pd(NO_2)_2$ (Mann, Crowfoot, Gattiker, and Wooster, *J.*, 1935, 1642) and their *trans*-isomers are the only known exceptions. The formation of these *cis*-palladous diamines has been investigated recently by Jonassen and Cull (*J. Amer. Chem. Soc.*, 1951, **73**, 274). There is also some evidence that $(AsMe_3)_2PdCl_2$ may exist in the crystal as the *cis*-isomer (Mann and Purdie, *J.*, 1935, 1549). All the remaining complexes of the type L_2PdX_2, whether L is an amine, trialkylphosphine, trialkylarsine, dialkyl sulphide, or dialkyl selenide, appear to have *trans*-configurations both in solution and in the solid state (Drew and Wyatt, *J.*, 1934, 56; Cox, Saenger, and Wardlaw, *J.*, 1934, 182; Mann and Purdie, *loc. cit.*). Their physical properties are similar to those of their *trans*-platinous analogues, but chemically they behave as a labile equilibrium mixture of *cis*- and *trans*-forms in which the *trans*-form predominates (*e.g.*, see Mann *et al.*, *J.*, 1935, 1642).

Our study of equilibria in the series of complexes $(MR_3)_2PtCl_2$ (M = P, As, or Sb, R = *n*-alkyl) in benzene solution (Part V, *J.*, 1952, 273; Part VI *) shows that the *cis*-configuration is increasingly favoured as M is replaced in the order As<P≪Sb. The

* Part VI, *J.*, 1952, 4300.

very much greater equilibrium concentration of *cis*-isomers in the stibine platinous series of complexes is due to the much smaller entropy differences between the isomers in this series than between isomers in the corresponding phosphorus and arsenic series. This is an effect we might expect when any similar series of stibine complexes is compared with the phosphorus and arsenic analogues. We have, therefore, investigated the palladous complexes, $(MR_3)_2PdCl_2$, and find that all the lower alkyl stibine complexes give benzene solutions containing a measurable quantity of the *cis*-isomer in labile equilibrium with its *trans*-isomer.

cis-Isomers are most easily distinguished from their *trans*-isomers by the exceptionally large dielectric constants of their solutions, a consequence of their high electric dipole moments. Thus in the platinous series, $(MR_3)_2PtCl_2$ (M = P, or As), the *cis*-isomers have dipole moments of about 10 D (Jensen, *Z. anorg. Chem.*, 1936, **229**, 225). The *trans*-isomers must have zero moments, but when they are measured and computed in the usual manner a value of about 1 D is found in both the platinous and the palladous series. This apparent moment is due to the exceptionally large atom polarisation of compounds such as those under consideration, which have highly dipolar bonds (Sutton *et al.*, *J.*, 1938, 1254, 1269; Charles and Freiser, *J. Amer. Chem. Soc.*, 1951, **73**, 5223). Jensen found it necessary to assume an atom polarisation of about 20% of the electron polarisation (instead of the usual 0—5%) in order that a number of symmetrical *trans*-platinous complexes should have zero moment. If a similar assumption is made regarding the palladous complexes, then the moments of $(PEt_3)_2PdCl_2$ and $(AsEt_3)_2PdCl_2$, computed to be 1·05 and 1·04 D, respectively (Mann and Purdie, *loc. cit.*), are in fact zero. The quantity of *cis*-isomer in solutions of these palladous complexes is thus too small to have any significant effect on the apparent dipole moment.

It is not possible to obtain accurate dipole moments of co-ordination compounds with small moments from solution measurements. Therefore, we have compared the increment ($\Delta\varepsilon$) in dielectric constant produced by dissolving various quantities of the complex in 43·36 g. of benzene at 25°. The quotient $\Delta\varepsilon/f$, where f is the mol.-fraction of solute, is constant to within our limits of accuracy in the dilute solutions we used.

All the platinous complexes of type $(MR_3)_2PtCl_2$ (where R = Et or Pr^n, and M = P, As, or Sb) of *trans*-configuration give values of $\Delta\varepsilon/f$ lying between 1·8 and 2·8 (Table 3). Those of *cis*-configuration give values in the range 150—170 (Table 4). The values of $\Delta\varepsilon/f$ for a number of palladium complexes are listed for comparison in Table 1. None of these complexes has a purely *cis*-configuration. The solutions of the phosphine and arsine complexes, which we know contain such a small amount of *cis*-isomer that it cannot be detected by this method, have values of $\Delta\varepsilon/f$ in the region 2—3; on the other hand, the stibine complexes in solution give values ranging from 8·5 to 70. Obviously, the benzene solutions of the stibine palladous complexes must contain an appreciable quantity of the *cis*-isomer in equilibrium with its *trans*-isomer.

TABLE 1. *$\Delta\varepsilon/f$ of the palladous complexes, $(MR_3)_2PdCl_2$, and percentages of* cis-$(SbR_3)_2PdCl_2$ *and of* cis-$(SbR_3)_2PtCl_2$ *in equilibrium with their* trans-*isomers in benzene solution at 25°.*

	R =				
M	Me	Et	Pr^n	Bu^n	Ph
P	—	2·7 †	2·6	2·2	—
As	—	2·9 †	2·9	2·6	—
		3·0			
Sb	60—70 *	12·2	8·7	8·6	25·6
% of *cis*-$(SbR_3)_2PdCl_2$	~40 *	6·0	3·8	3·7	14·6
% of *cis*-$(SbR_3)_2PtCl_2$ ...	~80 *	34·4	20·0	20·7	— *

* Accurate values are not possible because these complexes are too insoluble in benzene at 25°.
† Calc. from Mann and Purdie's measurements, *loc. cit.*

If we assume that solutions of pure *cis*-$(SbR_3)_2PdCl_2$ would have a value of $\Delta\varepsilon/f$ of the order of 160 as in the platinous series, we can estimate roughly the percentages of *cis*-isomers in the equilibria. These are tabulated in Table 1 together with the corresponding values in the platinous series. They are found to vary with the size of alkyl group in the same way as they do in the platinous series, where we know that we are measuring equilibria

between *cis*- and *trans*-isomers. This supports the view that the high values of $\Delta\varepsilon/f$ in the stibine palladous series are due to equilibria between *cis*- and *trans*-forms; however, the position of equilibrium in the palladous series is shifted well to the *trans*- side. $(SbPh_3)_2PdCl_2$ contains about 14% of its *cis*-isomer in equilibrium with its *trans*-isomer but its almost insoluble platinum analogue has not been investigated.

In the platinous series of complexes $(MR_3)_2PtCl_2$ (M = P, As, or Sb) we know that the *cis*- is always much less soluble than its *trans*-isomer, especially in non-polar solvents. Thus, when they are in labile equilibrium, the *cis*-isomer separates first on evaporation of benzene or light petroleum solutions. This occurs even when the equilibrium concentration of *cis*-isomer is only 0·2% of that of its *trans*-isomer, as it is in the case of $(AsPr_3)_2PtCl_2$ (Chatt and Wilkins, *J.*, 1951, 2532). We should expect similar solubility relations to exist in the palladous series. Thus only the solid *cis*-isomers $(SbR_3)_2PdCl_2$ should be capable of isolation from solution. It is obvious that this is so when we compare the physical properties of the solid palladous complexes in the series $(MR_3)_2PdCl_2$ with one another and with those of their platinum analogues. The *n*-propyl compounds are compared in Table 2. It shows that solid $(SbPr_3)_2PdCl_2$ is analogous to *cis*-$(SbPr_3)_2PtCl_2$

TABLE 2.

Substance	M. p.	Colour	Solubility in light petroleum
cis-$(PPr_3)_2PtCl_2$	149°	White	Insoluble
cis-$(AsPr_3)_2PtCl_2$	127	Very pale yellow	Insoluble
cis-$(SbPr_3)_2PtCl_2$	80	Pale yellow	Insoluble
trans-$(PPr_3)_2PtCl_2$	85	Pale yellow	Soluble
trans-$(AsPr_3)_2PtCl_2$	51	Yellow	Very soluble
$(PPr_3)_2PdCl_2$	96	Yellow	Very soluble
$(AsPr_3)_2PdCl_2$	55	Orange-yellow	Extremely soluble
$(SbPr_3)_2PdCl_2$	66 *	Yellow	Extremely soluble † to give a red solution

The arrows indicate the direction of increasing m. p., colour, and solubility, the last relating to organic solvents generally. * Melts with decomp.

† Finely divided $(SbPr_3)_2PdCl_2$ dissolves very much more slowly than either its phosphorus or its arsenic analogue although finally a very concentrated red solution is obtained. Obviously, the yellow solid which has a *cis*-configuration and low solubility dissolves slowly, but because it isomerises in solution to the very soluble red *trans*-isomer, concentrated solutions are produced. *cis*-$(SbPr_3)_2PtCl_2$ behaves similarly on dissolving in benzene but it isomerises sufficiently slowly for the rate to be measured. Eventually it gives an orange-red solution containing 80% of the solute as the *trans*-isomer. All the other complexes dissolve without change of colour.

whereas solid $(PPr_3)_2PdCl_2$ and solid $(AsPr_3)_2PdCl_2$ are analogous to *trans*-$(PPr_3)_2PtCl_2$ and *trans*-$(AsPr_3)_2PtCl_2$, respectively. Generally, in series of complexes of this type, the palladous complexes are more highly coloured and more soluble in all solvents than the corresponding platinous complexes. There can be little doubt that the crystalline tertiary stibine palladous chloride complexes have a *cis*-configuration, but isomerise immediately in benzene solution at room temperature.

EXPERIMENTAL

Microanalyses are by Mr. W. Brown, of these laboratories.

Preparation of Compounds.—The palladous chloride complexes were prepared by shaking aqueous ammonium palladochloride with the tertiary phosphine, arsine (Mann and Purdie, *J.*, 1935, 1549), or stibine (Morgan and Yarsley, *J.*, 1925, 184; Jensen, *loc. cit.*). The tertiary stibine complexes, $(SbR_3)_2PdCl_2$, have low stability and their ease of decomposition increases rapidly from R = Me to R = Bu. The compounds used were as follows: Bistrimethylstibinedichloropalladium had decomp. pt. 150—165° (Found: C, 13·7; H, 3·4. Calc. for $C_6H_{18}Cl_2PdSb_2$: C, 14·1; H, 3·6%); bistriethylstibinedichloropalladium had decomp. pt. 90—91° (Jensen, *loc. cit.*, records *ca.* 90°). The compounds decompose without melting.

Bistri-n-propylstibinedichloropalladium. Tri-*n*-propylstibine (7·0 g.) was shaken for 5 minutes under nitrogen with ammonium palladochloride (4·0 g.) in water (75 c.c.) at 0°. The yellow product was washed with ice-cold water by decantation and collected on a filter. It was dried, and extracted with ligroin (b.p. 100—120°; 100 c.c.), and the bright red extract filtered and cooled to −70°. The yellow solid which separated was quickly filtered off, the recrystallisation repeated, and the twice-recrystallised *complex* dried at 0·01 mm. It had m. p. 66—68°

(decomp.; efferv.) (Found: C, 31·8; H, 6·2. $C_{18}H_{42}Cl_2PdSb_2$ requires C, 31·8; H, 6·2%). This dry product darkens slowly on storage, the darkening becoming obvious after 3—4 days. The bright yellow *n*-butyl analogue, m. p. 64—65° (decomp.), was prepared similarly but darkened much more rapidly.

The samples of ethyl and propyl platinous compounds used in these experiments were the same as those described in Parts III, V, and VI (*J.*, 1951, 2532; *locc. cit.*). Bistri-*n*-butylstibinedichloroplatinum was prepared as described by Jensen (*loc. cit.*) and had m. p. 63—63·5° (Jensen gives 62—63°).

Bistriphenylstibinedichloropalladium. Triphenylstibine (1·2 g.) in ethanol (20 c.c.) was shaken with ammonium palladochloride (0·5 g.) in water (15 c.c.) for ½ hr. at room temperature. The yellow *complex* was filtered off, dried, and purified by dissolution in warm chloroform, filtration (charcoal), and crystallisation by addition of ether; it decomposed at *ca.* 140° (Found: C, 48·5; H, 3·4. $C_{36}H_{30}Cl_2PdSb_2$ requires C, 48·9; H, 3·4%).

Measurements of Dielectric Constants.—The dielectric constants of the benzene solutions at 25° were determined as described in Part VI (*loc. cit.*) and are recorded in Tables 3—5, where W = weight of substance dissolved in 43·36 g. of benzene, f = mol.-fraction of substance, ΔC = increase in capacity of the electrical condenser containing solution as dielectric over its capacity with benzene as dielectric, ε = dielectric constant of solutions given by

TABLE 3. $\Delta\varepsilon/f$ *of* trans-$(MR_3)_2PtCl_2$ *in benzene solutions at* 25°.

Substance	W, mg.	10^5f	ΔC, $\mu\mu$F	ε	$10^2\Delta\varepsilon$	$\Delta\varepsilon/f$
$(PEt_3)_2PtCl_2$	609·0	217·8	0·231	2·2779	0·52	2·39
$(AsEt_3)_2PtCl_2$	998·1	303·7	0·366	2·2810	0·83	2·73
	2525·4	764·8	0·917	2·2934	2·07	2·71
	3024·4	914·5	1·112	2·2978	2·51	2·74
$(PPr_3)_2PtCl_2$	782·0	239·6	0·198	2·2772	0·45	1·88
	1005·0	307·7	0·251	2·2784	0·57	1·85
	1277·4	390·8	0·337	2·2803	0·76	1·94
$(AsPr_3)_2PtCl_2$	1003·6	267·3	0·287	2·2792	0·65	2·43
	3037·2	804·6	0·861	2·2921	1·94	2·41

TABLE 4. $\Delta\varepsilon/f$ *of* cis-$(MR_3)_2PtCl_2$ *in benzene solutions at* 25°.

Substance	W, mg.	10^5f	ΔC, $\mu\mu$F	ε	$10^2\Delta\varepsilon$	$\Delta\varepsilon/f$
$(PEt_3)_2PtCl_2$	41·8	14·98	1·112	2·2978	2·51	168
	42·6	15·27	1·129	2·2982	2·55	167
	52·1	18·67	1·376	2·3037	3·10	166
	54·0	19·35	1·436	2·3051	3·24	167
$(AsEt_3)_2PtCl_2$	36·5	11·14	0·832	2·2915	1·88	169
	37·6	11·47	0·852	2·2919	1·92	167
	43·2	13·18	0·967	2·2945	2·18	165
	59·0	18·00	1·340	2·3029	3·02	168
$(SbEt_3)_2PtCl_2$	89·6	23·59	1·630	2·3095	3·68	156
	96·1	25·30	1·723	2·3116	3·89	154
	99·5	26·20	1·792	2·3131	4·04	154
$(PPr_3)_2PtCl_2$	35·7	10·96	0·789	2·2905	1·78	162
	40·4	12·41	0·898	2·2930	2·02	163
$(AsPr_3)_2PtCl_2$	31·0	82·79	0·597	2·2862	1·35	163
	41·5	11·08	0·805	2·2909	1·82	164
	93·6	24·99	1·832	2·3140	4·13	165
$(SbPr_3)_2PtCl_2$	102·4	24·01	1·723	2·3116	3·89	162
	212·1	49·71	3·578	2·3534	8·07	162
$(SbBu_3)_2PtCl_2$	96·3	20·35	1·462	2·3057	3·30	162
	106·8	22·57	1·620	2·3092	3·65	162

$\varepsilon = 1 + 1{\cdot}2727(56{\cdot}43 + \Delta C)(56{\cdot}43)^{-1}$ (2·2727 is the dielectric constant of benzene and 56·43 a constant of our apparatus), and $\Delta\varepsilon = \varepsilon - 2{\cdot}2727$.

The percentages of *cis*-isomers in the solutions of the stibine palladous complexes, recorded in Table 5, were calculated from $\Delta\varepsilon/f$ by means of the relation $\Delta\varepsilon/f = 160f_c/f + 2{\cdot}9f_t/f$, where f_c = mol.-fraction of *cis*-isomer, f_t = that of *trans*-isomer, and $f = f_c + f_t$; 160 is the probable value of $\Delta\varepsilon/f_c$ of a solution of the pure *cis*-isomer, assumed on the basis of our measurements in the platinous series (Table 4), and 2·9 is the probable value of $\Delta\varepsilon/f_t$ of a solution of the pure *trans*-isomer, assumed on the basis of our measurements in the palladous series of phosphine and arsine

complexes (Table 5). We consider the uncertainly in these assumptions to give a possible error of ±20% of their value to the figures in the last column of Table 5.

TABLE 5. $\Delta\varepsilon/f$ *of* $(MR_3)_2PdCl_2$ *and percentage of* cis-*isomer in equilibrium with the* trans-*isomer in benzene solution at* 25°.

Substance	*W*, mg.	10^5f	ΔC, $\mu\mu$F	ε	$10^2\Delta\varepsilon$	$\Delta\varepsilon/f$	*cis*-isomer, %
$(PEt_3)_2PdCl_2$	—	505·8	—	2·2865	1·38	2·73 *	~0
$(AsEt_3)_2PdCl_2$	996·4	356·4	0·479	2·2835	1·08	3·03	~0
	—	542·1	—	2·2882	1·55	2·86 *	
$(PPr_3)_2PdCl_2$	997·6	359·5	0·413	2·2820	0·93	2·59	~0
$(AsPr_3)_2PdCl_2$	502·8	154·3	0·201	2·2772	0·45	2·92	~0
	998·1	305·9	0·393	2·2816	0·89	2·91	
$(PBu_3)_2PdCl_2$	833·5	257·2	0·254	2·2784	0·57	2·22	~0
$(AsBu_3)_2PdCl_2$ ...	990·9	265·7	0·301	2·2795	0·68	2·56	~0
$(SbMe_3)_2PdCl_2$ ...	3·0	1·057	0·033	2·2734	0·07	66	40
	5·3	1·867	0·053	2·2739	0·12	64	
$(SbEt_3)_2PdCl_2$	194·4	58·78	0·320	2·2799	0·72	12·2	6·0
$(SbPr_3)_2PdCl_2$	499·6	132·2	0·508	2·2842	1·15	8·70	3·8
$(SbBu_3)_2PdCl_2$ ...	997·0	234·6	0·894	2·2929	2·02	8·61	3·7
$(SbPh_3)_2PdCl_2$ ...	195·7	398·8	0·452	2·2829	1·02	25·6	14·6

* Calculated from Mann and Purdie's measurements (*loc. cit.*).

The corresponding equilibrium percentages of *cis*-isomers in the platinous series, shown in Table 1, are known with much greater accuracy, except that of $(SbMe_3)_2PtCl_2$ which is almost insoluble in benzene. The value for $(SbEt_3)_2PtCl_2$ is taken from Part VI (*loc. cit.*); the equilibria in the propyl and butyl platinous series will be examined to find the heat and entropy effects of the isomerisations and will be reported later.

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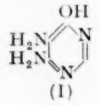
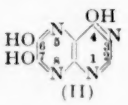
11. *Pteridine Studies. Part IV.* 4 : 6- and 4 : 7-Dihydroxypteridine.*

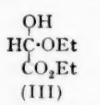
By ADRIEN ALBERT and D. J. BROWN.

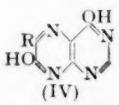
4 : 6-Dihydroxypteridine has been prepared from 4 : 6 : 7-trihydroxypteridine (II) by sodium amalgam, a reagent specific for the removal of a 7-hydroxy-group. The dihydroxypteridine produced by the action of ethyl glyoxylate on 4 : 5-diamino-6-hydroxypyrimidine (I) is shown to be the 4 : 6-derivative. 4 : 7-Dihydroxypteridine has been prepared by degrading 6-carbethoxymethyl-4 : 7-dihydroxypteridine obtained by condensing (I) with ethyl oxaloacetate.

STUDIES of the solubility and stability of pteridines (Part III*) necessitated the synthesis of 4 : 6- and 4 : 7-dihydroxy- and 4 : 6 : 7-trihydroxy-pteridine. The last-named (II) was readily prepared by condensation of 4 : 5-diamino-6-hydroxypyrimidine (I) and oxalic acid.


(I)


(II)


(III)


(IV)

The action of sodium amalgam in water on (II) gave 7 : 8-dihydro-4 : 6-dihydroxypteridine which was readily oxidized to 4 : 6-dihydroxypteridine. The orientation follows from analogy with 6 : 7-dihydroxypteridine from which sodium amalgam specifically removes the 7-hydroxy-group (Part II, *J.*, 1952, 1620). 4 : 6-Dihydroxypteridine was the

* Part III, *J.*, 1952, 4219.

sole product isolated from the reaction of (I) with ethyl glyoxylate hemiacetal (III) at pH 7, 6, 5, or 0, despite the fact that 4 : 5-diaminopyrimidine gave mainly 7-hydroxypteridine at pH 6, and 6-hydroxypteridine at pH 0 (Part II). Moreover, the use of ethyl glyoxylate, as such, produced no 4 : 7-dihydroxypteridine.

Potentiometric titration of the more acidic of the two hydroxyl groups in 4 : 6-dihydroxypteridine gave a hysteresis loop similar to that of 6-hydroxypteridine (illustrated

Pteridine derivative	pK_a (in H_2O) and concn. (20°)		R_F [c]	Spectrosopy in H_2O $\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$ (mol.)	pH
4 : 6 : 7-Trihydroxy-	—	—	0·05 [d]	—	—	—
(polyanion)	—	—	—	225; 319 + 330	4·45; 4·10 + 4·11	13·0
4 : 6-Dihydroxy- (+1H_2O)	—	—	0·50 [e]	<220; 270; 356	>4·14; 4·02; 3·38 [f]	4·0
(monoanion)	6·08[a] (±0·02)	(M/1000)	—	<220; 241; 280; 359	<3·9; 3·88; 4·03; 3·83 [g]	7·90
(dianion)	9·73 (±0·04)	(M/1000)	—	<220; 254; 367	>3·9; 4·18; 3·84 [g]	13·0
4 : 7-Dihydroxy-	—	—	0·30	<220; 285; 328	>4·6; 3·82; 3·94	4·0
(monoanion)	6·08 (±0·02)	(M/750)	—	227; 289; 326	4·38; 3·79; 3·95	7·9
(dianion)	9·62 (±0·03)	(M/750)	—	231; 329	4·41; 4·00	13·0
4 : 7-Dihydroxy-6-methyl- (+1H_2O)	—	—	0·45	<220; 285; 321	>4·25; 3·95; 4·00	4·50
(monoanion)	6·82 (±0·01)	(M/150)	—	225; 324	4·40; 4·04	8·44
(dianion)	10·02 (±0·06)	(M/150)	—	— [h]	—	—
6-Formyl-4 : 7-dihydroxy- (+0·9H_2O)	—	—	0·50	<220; 285; 329	>4·2; 3·80; 3·98	3·9
(monoanion)	5·93 (±0·02)	(M/100)	—	—	—	—
(dianion)	9·31 (±0·03)	(M/100)	—	—	—	—
oxime	—	—	0·20	—	—	—
4 : 7-Dihydroxy-6-carboxylic acid (+1H_2O)	—	—	0·07 [f]	—	—	—
(monoanion)	*ca.* 3 [b]	(M/750)	—	224; 288; 336	4·15; 3·78; 4·02	4·85
(dianion)	6·69 (±0·01)	(M/750)	—	226; 293; 331	4·40; 3·82; 4·01	8·37
(trianion)	10·05 (±0·05)	(M/750)	—	—	—	—
6-Carbethoxymethyl-4 : 7-dihydroxy-	—	—	0·70	<220; 287; 327; 385 [g]	>4·1; 3·84; 4·03; 2·38	4·00
(monoanion)	6·23 (±0·08)	(M/500)	—	—	—	—
(dianion)	9·62 (±0·06)	(M/500)	—	—	—	—
6-Carboxymethyl-5 : 6-dihydro-4 : 7-dihydroxy-	—	—	0·45	—	—	—
(monoanion)	4·49 (±0·07)	(M/500)	—	<220; 276; 325	>4·0; 3·80; 3·73	6·52
(dianion)	8·59 (±0·07)	(M/500)	—	—	—	—
(trianion)	*ca.* 11	(M/500)	—	—	—	—
5 : 6-Dihydro-4 : 7-dihydroxy-6-methyl-	—	—	0·65	<220; 274; 323	>4·2; 3·79; 3·71	6·0
(monoanion)	8·43 (±0·03)	(M/500)	—	—	—	—
(dianion)	11·40 (±0·04)	(M/500)	—	—	—	—

[a] Rapid back-titration (to forestall formation of pseudo-acid). [b] Back-titration (to forestall precipitation). [c] In butanol–5N-acetic acid (2 : 1) by descending method, 4-hydroxypteridine (R_F 0·50) and picric acid (R_F 0·80) being used as controls. Papers viewed in light of 254 mμ. [d] Applied as the Na salt. [e] Also a small spot at 0·05. [f] Applied as the NH_4 salt. This is a strong acid; hence the spot consists of two zones, (*a*) the violet-fluorescing neutral molecule (which is photostable) and (*b*) the darkly-absorbing anion (which becomes yellow on irradiation). When the paper was sprayed with 0·1N-HCl before exposure to ultra-violet light, only (*a*) appeared. Likewise, this substance gave two spots in 3% aq. NH_4Cl, but only one if HCl were also present. [g] Shoulder. [h] Landauer (*loc. cit.*) obtained for the dianion: 227, 327 mμ (4·36; 4·05) at pH 13. [i] Change in ε at any part of the curve not more than 3% after 24 hours at 20°. [j] No significant change in ε at any part of the curve after 24 hours at 20°.

in Part II). Because 4- and 7-hydroxypteridine do not show hysteresis, this phenomenon confirms the 4 : 6- (as opposed to the 4 : 7-)orientation. 4 : 6-Dihydroxypteridine has no evident basic properties (it is no more soluble in boiling N-mineral acids than in water); this supports the explanation of the origin of basic properties in 6-hydroxypteridine, given in Part II.

On paper chromatography, this dihydroxypteridine gives a single spot in dimethyl-

formamide (90% aqueous) but two spots (see Table, p. 75) in butanol–acetic acid. These two appeared even when sodium sulphide was added to the solvent (to prevent formation of complexes with metals possibly present in the paper, see Table 3 of Part III). When both spots were cut out and sewn, side by side, on a new piece of paper and re-run in butanol–acetic acid, each produced *two* spots corresponding in R_F and fluorescence to the original two spots. It would appear that the tautomers of 4 : 6-dihydroxypteridine are separated during paper chromatography in this solvent.

Ethyl sodio-oxaloacetate gave 6-carbethoxymethyl-4 : 7-dihydroxypteridine (IV; R = $CH_2 \cdot CO_2Et$) when heated with (I) in acetic acid. The hydroxy-group was assigned to the 7- (rather than the 6-)position because 7-hydroxypteridines are exclusively formed when other 4 : 5-diaminopyrimidines are condensed with ethyl oxaloacetate in the absence of mineral acid (Tschesche, Köhncke, and Korte, *Z. Naturforsch.*, 1950, **5***b*, 132; Elion, Hitchings, and Russell, *J. Amer. Chem. Soc.*, 1950, **72**, 78), and this was confirmed by degradation to a dihydroxypteridine different from 4 : 6-dihydroxypteridine.

Alkaline hydrolysis of the ester gave 6-carboxymethyl-4 : 7-dihydroxypteridine, isolated by acidification at about 0°. Acidification at higher temperatures brought about decarboxylation to 4 : 7-dihydroxy-6-methylpteridine (IV; R = Me) (Landauer, Thesis, London, 1951; Rydon and Landauer, in preparation). It was hoped to remove the 7-hydroxyl group from this substance by sodium amalgam; instead, 5 : 6-dihydro-4 : 7-dihydroxy-6-methylpteridine was formed. The hydrogen atoms are assigned positions 5 and 6 from analogy with the alkaline reduction of 7-hydroxypteridine (Albert, Brown, and Cheeseman, *J.*, 1952, 1620). Clearly, the 7-position is not hydrogenated because *two* acidic groups are demonstrable (see Table 1). Similarly, the action of sodium amalgam on (IV; R = $CH_2 \cdot CO_2Et$) gave 6-carboxymethyl-5 : 6-dihydro-4 : 7-dihydroxypteridine. Both these dihydro-compounds were transformed into 4 : 7-dihydroxy-6-methylpteridine by cold potassium permanganate solution. The three known examples of pteridines which have lost the hydroxy-group from the 7-position on treatment with sodium amalgam have all borne a further hydroxy-group in the 6-position and this may prove to be a necessary condition.

Attempts to oxidize the 6-methyl group with selenium dioxide or potassium permanganate resulted in destruction of the entire molecule, even under conditions satisfactory for other 6-methylpteridines (Tschesche, Köhncke, and Korte, *loc. cit.*; Cain, Mallette, and Taylor, *J. Amer. Chem. Soc.*, 1948, **70**, 3026). Moreover, the methyl group did not combine with benzaldehyde at 155° in acetic anhydride. However, no difficulty was experienced in brominating (IV; R = Me) to 6-dibromomethyl-4 : 7-dihydroxypteridine, which was readily hydrolysed to 6-formyl-4 : 7-dihydroxypteridine. The rather high solubility of this aldehyde in water (in spite of the presence of three hydrogen-bonding groups) may be due to internal hydrogen-bonding (see Part III for a discussion of the factors governing solubility in this series). The aldehyde was oxidized to the carboxylic acid by cold aqueous potassium permanganate.

This acid is rapidly decarboxylated at 260° to 4 : 7-dihydroxypteridine, which is stable and shows no hysteresis during titration. The acid can be readily decomposed in two other ways: by exposure to daylight, whereupon it rapidly becomes brown; and by boiling it with water for 15 minutes, whereupon a colourless substance is formed having an intense violet fluorescence, visible in daylight. This fluorescent substance could not be separated from the acid and is known only through its characteristic spot on the paper chromatogram (R_F 0·30 in butanol–acetic acid). It is also formed when the acid is warmed with N-sodium hydroxide, but boiling N-hydrochloric acid or cold N-ammonia have no effect. When the acid was heated for 7 hours with water at 200°, two new spots appeared (R_F 0·65 and 0·80), both fluorescing strongly. Such intense violet fluorescence is common among pyrazines, rare among pteridines, and unknown in the pyrimidine series. The pattern of ring-opening in 4-hydroxypteridines (see Part III) suggests that these three substances may be derivatives of 2-aminopyrazine-3-carboxylic acid : this will be further investigated.

Physical properties of the substances described in this paper are listed in the Table (p. 75). The ionization constants of 4 : 6- and 4 : 7-dihydroxypteridine are unusually

close for isomerides in this series, but the behaviour during titration is different (see above). The spectra of substances containing both a 4- and a 7-hydroxy-group are very similar, a variety of substituents in the 6-position having little effect. Unlike the four monohydroxypteridines and the two dihydroxypteridines previously described (*J.*, 1951, 474; 1952, 1620), 4 : 7-dihydroxypteridine does not considerably increase the wave-length of maximum absorption in passing from the neutral molecule to the monoanion, or again upon passing from the monoanion to the dianion.

The spectra of 4 : 6-dihydroxypteridine are entirely different from those of these 4 : 7-dihydroxy-derivatives. The neutral molecule, as measured, is substantially at equilibrium because little change occurred during 24 hours. The same spectrum was obtained when the substance was dissolved in 2 equivalents of alkali and added to pH 4 buffer, or when a solution (pH 5) in boiling water was added to the buffer; in the former case tautomerization must have been practically complete in less than 15 minutes.

Experimental

M. p.s are uncorrected. In the case of substances that have no definite m. p., the yield refers to the stage at which they became chromatographically homogeneous (on paper). Microanalyses were by Mr. P. R. W. Baker, Beckenham.

4 : 6 : 7-*Trihydroxypteridine* (II).—4 : 5-Diamino-6-hydroxypyrimidine (I) (2·5 g.; *J.*, 1951, 474) and oxalic acid dihydrate (17·6 g., 7 equiv.) were finely powdered and heated to 165° during 0·5 hour, and kept at 165° for 2 hours. The product was boiled with water (180 ml.) containing 6N-sodium hydroxide (40 ml.) and filtered. The filtrate was brought to pH 2 with 10N-hydrochloric acid (about 20 ml.). The white crystals were washed with boiling water, dried at 110° (yield 3·45 g. 95%), and recrystallized as the potassium salt from 40 parts of water containing 7 equivs. of potassium carbonate. 4 : 6 : 7-*Trihydroxypteridine* (90%). recovered from a hot solution of the crystals by acidification, was unchanged at 350°, not appreciably soluble in boiling dimethylformamide, 2-methoxyethanol, pyridine, formic acid, or 5N-hydrochloric acid, but soluble in 400 parts of formamide at 170° and in 7000 parts of boiling water (Found : C, 40·0; H, 2·3; N, 31·8. $C_6H_4O_3N_4$ requires C, 40·0; H, 2·2; N, 31·1%).

7 : 8-*Dihydro*-4 : 6-*dihydroxypteridine*.—4 : 6 : 7-Trihydroxypteridine (1·8 g.), finely powdered, was gently shaken with water (25 ml.) while sodium amalgam (24 g.; 4%) was added during 15 minutes at 50°. The liquid was adjusted to pH 4·5 with acetic acid (3 ml.) and 5N-sulphuric acid, then brought to the boil and filtered at once. The residue (90%) was recrystallized from about 2000 parts of boiling water, giving 7 : 8-*dihydro*-4 : 6-*dihydroxypteridine*, almost insoluble in boiling dimethylformamide, other organic solvents, or boiling N-hydrochloric acid (Found : N, 33·3. $C_6H_6O_2N_4$ requires N, 33·7%).

4 : 6-*Dihydroxypteridine*.—(a) *By oxidation of the above dihydropteridine.* To 7 : 8-dihydro-4 : 6-dihydroxypteridine (1·2 g.) and sodium hydroxide (0·52 g.) in cold water (65 ml.) was added 0·1M-potassium permanganate (46 ml., 1 equiv.) during 10 minutes. The mixture was centrifuged and the residue boiled with water (15 ml.). The combined liquids were adjusted to pH 4, giving 4 : 6-dihydroxypteridine (70%). It was purified as was the following specimen and had identical properties.

(b) *Direct synthesis.* 4 : 5-Diamino-6-hydroxypyrimidine (I) (5 g., 0·04 mole) was dissolved in boiling 2N-sulphuric acid (80 ml.). Ethyl glyoxylate hemiacetal (9 g., 0·06 mole; Rigby, *J.*, 1950, 1912) was added. The mixture was kept in boiling water for 1 hour, then cooled and filtered after 4 hours. The solid was recrystallized from boiling water (300 parts), giving yellow crystals (3·6 g.), which were dissolved in boiling water (18 ml.) containing potassium carbonate (10·8 g.). The solution was refrigerated, and the potassium salt filtered off and dissolved in boiling water (40 ml.). The solution, brought to pH 4 with acetic acid, gave pale yellow 4 : 6-*dihydroxypteridine* (52%), recrystallized from 300 parts of water, soluble in about 500 parts of boiling butanol, very soluble in formylmorpholine, and almost insoluble in pyridine acetic acid, dimethylformamide; it darkens at 320° but is unmelted at 350° (Found, for material dried at 110° : C, 39·7; H, 3·4; N, 30·9. $C_6H_4O_2N_4,H_2O$ requires C, 39·6; H, 3·3; N, 30·8%). The yellow colour (and spectrum) persists after chromatography on an alumina column in 0·5N-ammonia (cf. the 4 : 7-isomer below). A solution in borate buffer (pH 8·0) gives a reddish-orange colour with ferrous sulphate.

6-*Carbethoxymethyl*-4 : 7-*dihydroxypteridine*.—Ethyl sodio-oxaloacetate (22·5 g.), 4 : 5-diamino-6-hydroxypyrimidine (12·6 g.), and acetic acid (100 ml.) were heated at 100° for an

hour, with vigorous shaking until a clear solution was obtained (5 minutes). Water (100 ml.) was added and the mixture was chilled for an hour. The solid was washed with water (100 ml.), then with alcohol (50 ml.), and dried at 120° (yield, 70%). *6-Carbethoxymethyl-4 : 7-dihydroxypteridine* crystallized from 18 parts of pyridine (75% recovery after 24 hours' chilling) as yellow needles, decomp. *ca.* 250°. It requires more than 250 parts of boiling water for dissolution (Found : C, 48·4; H, 4·1; N, 22·3. $C_{10}H_{10}O_4N_4$ requires C, 48·0; H, 4·0; N, 22·4%).

6-Carboxymethyl-4 : 7-dihydroxypteridine.—6-Carbethoxymethyl-4 : 7-dihydroxypteridine (0·5 g.) was refluxed with 2·5N-sodium hydroxide (5 ml., 6 equiv.) for 1 hour. The solution was cooled in ice and adjusted to pH 1·5 (metanil yellow) with N-sulphuric acid. The precipitate was filtered off after 3 hours and dried at 20° ($CaCl_2$), giving the acid as a canary-yellow powder (80%) which was decarboxylated at once by warm water and other solvents, and on attempted drying at 110° (Found, for material dried at 20°/0·01 mm. : C, 43·4; H, 2·8; N, 25·1. $C_8H_6O_4N_4$ requires C, 43·2; H, 2·7; N, 25·2%). The R_F is 0·60. The sodium and the potassium salt are very soluble in water.

4 : 7-Dihydroxy-6-methylpteridine.—6-Carbethoxymethyl-4 : 7-dihydroxypteridine (10 g.) was refluxed for 1 hour with 2·5N-sodium hydroxide (100 ml.), then treated with 5N-sulphuric acid (80 ml.) and refluxed for 5 minutes. The suspension, kept at room-temperature overnight, was filtered and the crystals were rubbed in a mortar with water (10 ml.), filtered off, and dried at 110° (in a large dish because they puff up), giving 4 : 7-dihydroxy-6-methylpteridine monohydrate (90%), which from 65 parts of boiling water gave colourless crystals which darkened at 340° but did not melt at 350° (Found, for material dried at 110° : C, 43·2; H, 3·9; N, 28·4. Calc. for $C_7H_6O_2N_4,H_2O$: C, 42·85; H, 4·1; N, 28·6%). It is soluble in 55 parts of boiling acetic acid with good temperature gradient, but only moderately soluble in butanol or dry pyridine, very soluble in cold 10N-(but not in N-)hydrochloric acid.

5 : 6-Dihydro-4 : 7-dihydroxy-6-methylpteridine.—4 : 7-Dihydroxy-6-methylpteridine monohydrate (0·98 g.,) water (6 ml.), and 4% sodium amalgam (12 g.) were gently stirred at 50—60° for 15 minutes. The liquid was taken to pH 5 with acetic acid and refrigerated overnight. The solid, recrystallized from 200 parts of boiling water and dried at 110°, gave *5 : 6-dihydro-4 : 7-dihydroxy-6-methylpteridine* (90%), decomp. > 300°, poorly soluble in boiling N-hydrochloric acid, pyridine, or butanol, but readily soluble in boiling 5N-hydrochloric acid, acetic acid, dimethylformamide, and cold N-sodium hydroxide (Found : C, 46·9; H, 4·5; N, 31·0. $C_7H_8O_2N_4$ requires C, 46·7; H, 4·5; N, 31·1%). To this substance (0·45 g.), in cold N-sodium hydroxide (6 ml.), was added 0·1M-potassium permanganate (17 ml.) during 10 minutes. The mixture was centrifuged, and the manganese dioxide boiled with 0·1N-sodium hydroxide (6 ml.). The combined supernatant liquids were taken to pH 5 with acetic acid, and then deposited 4 : 7-dihydroxy-6-methylpteridine (85%).

6-Carboxymethyl-5 : 6-dihydro-4 : 7-dihydroxypteridine.—The ester (IV; R = $CH_2{\cdot}CO_2Et$) (1 g.) was suspended in water (6 ml.); sodium amalgam (12 g.; 4%) was added with gentle shaking, the temperature being kept at 50—60°. The liquid was acidified to pH 4 with acetic acid. The solid, recrystallized from water, gave *6-carboxymethyl-5 : 6-dihydro-4 : 7-dihydroxypteridine* (80%), soluble in 200 parts of boiling water, m. p. 320° (with effervescence) (Found : C, 43·1; H, 3·6. $C_8H_8O_4N_4$ requires C, 42·9; H, 3·6%). Potassium permanganate (as above) gave 4 : 7-dihydroxy-6-methylpteridine (85%).

6-Dibromomethyl-4 : 7-dihydroxypteridine.—To 4 : 7-dihydroxy-6-methylpteridine monohydrate (0·98 g.) in boiling acetic acid (55 ml.), bromine (2·1 g.) in acetic acid (5 ml.) was added and boiling was continued for 15 minutes. Next day, the *6-dibromomethyl-4 : 7-dihydroxypteridine hydrobromide* was filtered off and washed wel lwith acetic acid (yield, 1·87 g., 90%). It darkens at 215°, but is unmelted at 250° (Found : C, 20·3; H, 1·4; N, 13·5; Br, 56·7. $C_7H_4O_2N_4Br_2,HBr$ requires C, 20·2; H, 1·2; N, 13·4; Br, 57·5%).

6-Formyl-4 : 7-dihydroxypteridine.—The above hydrobromide (1·8 g.) was boiled with water (40 ml.) for 20 minutes. The solution was decolorized with carbon and kept at 0° for 2 hours, giving *4 : 7-dihydroxypteridine-6-aldehyde monohydrate* (85%), pale yellow crystals (decomp. about 320°) (from 33 parts of boiling water). It is only slightly soluble in boiling acetic acid, or dry pyridine and darkens if dried in air at 110° (Found, for material dried at 20°/0·1 mm. : C, 40·4; H, 2·95; N, 27·1. $C_7H_4O_3N_4,0{\cdot}9H_2O$ requires C, 40·4; H, 2·8; N, 26·9%). It does not reduce Fehling's solution, but blackens warm ammoniacal silver nitrate. The oxime (0·2 g.), prepared in the usual way, was recrystallized from pyridine trihydrate (15 ml.) as the pyridine salt which was dissolved in hot water (50 ml.). This solution was concentrated to half-volume in order to hydrolyse the salt and expel the pyridine. After cooling, 0·15 g. of *oxime* was obtained as yellow crystals which darken at 320° without melting. It is almost

insoluble in water and neutral organic solvents (Found, for material dried at 110°/0·01 mm.: C, 37·3; H, 2·8; N, 31·4. $C_7H_5O_3N_5,H_2O$ requires C, 37·3; H, 3·1; N, 31·1%).

4 : 7-*Dihydroxypteridine*-6-*carboxylic Acid*.—The finely powdered aldehyde (3·15 g.) was stirred with cold water (150 ml.), and dissolved by slow addition of N-sodium hydroxide (15 ml.). Kieselguhr (1 g.; Filter-Cel brand) was added, then 0·1M-potassium permanganate (100 ml., 1 equiv.) during 15 minutes. The mixture was centrifuged, and the sediment stirred with cold water (100 ml.) and recentrifuged. The combined supernatant liquids were taken to pH 2 (metanil-yellow) with 5N-sulphuric acid. After 1 day at 0°, the precipitate was washed, and dried at 110°, yielding pale yellow 4 : 7-*dihydroxypteridine*-6-*carboxylic acid monohydrate* (75%). This was purified by dissolution in cold water (200 ml.) with the aid of 6N-ammonia (2·4 ml.) and passage through aluminium oxide (10 × 2·5 cm.), followed by 0·1N-ammonia (200 + 200 ml.). The united percolates were brought to pH 4 with acetic acid, then (after clarification) to pH 2 with hydrochloric acid. The precipitate was washed and dried at 110°. The substance becomes faintly brown at about 260°. It is moderately soluble in dimethylformamide and in formylmorpholine but sparingly soluble in other organic solvents (Found, for material dried at 110°/0·01 mm.: C, 37·1; H, 2·6; N, 24·7. $C_7H_4O_4N_4,H_2O$ requires C, 37·2; H, 2·7; N, 24·8%). It is only slightly soluble in boiling 5N-sulphuric acid.

4 : 7-*Dihydroxypteridine*.—The foregoing acid (2·5 g.) was finely powdered and heated under nitrogen for an hour in a bath pre-heated to (and kept at) 265°. The residue was stirred with N-ammonia (30 ml.). The mixture was filtered, diluted to 75 ml., and poured on aluminium oxide (10 × 2·5 cm.), being followed by water (50 + 50 ml.). The alumina retained a yellow impurity of low R_F. The united percolates were acidified to pH 4·5 with acetic acid, giving 4 : 7-*dihydroxypteridine* (70%)., which recrystallized from 600 parts of boiling water. It remains almost unchanged at 350°, is almost insoluble in boiling acetic acid, pyridine, and dimethylformamide. It can be recrystallized from formylmorpholine (Found: C, 44·0; H, 2·5; N, 33·9. $C_6H_4O_2N_4$ requires C, 43·9; H, 2·45; N, 34·2%). It is no more soluble in boiling N-hydrochloric acid than in water. A solution in borate buffer (pH 8·0) gives an intense orange colour with ferrous sulphate.

We are grateful to Professor H. N. Rydon and Dr. Phyllis Landauer for directing our attention to 4 : 7-dihydroxy-6-methylpteridine which they were the first to synthesize. We thank Dr. L. N. Short for general supervision of the spectrophotometric work, Mr. E. P. Serjeant for potentiometric titrations and for skilled spectrophotometric assistance, and Mr. D. T. W. Light for the paper chromatography.

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12. *Ester and Lactone Linkages in Acidic Polysaccharides. Part I.*

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Simple carbohydrate esters and hexono- and urono-lactones with hydroxylamine under alkaline conditions yield hydroxamic acids which provide a basis for the estimation of these lactonised groups in natural products.

Uronolactones have been detected in dried specimens of various polyuronides.

HYDROXYLAMINE has been widely investigated as a means of detection and estimation of micro-amounts of carboxylic esters (Feigel, "Spot Tests," Elsevier, New York, 1939); these are very readily transformed into hydroxamic acids which give intensely coloured compounds with ferric salts. Hestrin (*J. Biol Chem.*, 1949, **180**, 249) used the method successfully for the quantitative assay of, notably, choline esters and Whittaker and Wijesundera (*Biochem J.*, 1951, **51**, 348) developed it for chromatographic separations. Its mechanism is considered to be analogous to that postulated for the formation of amides from esters by ammonia (Gordon, Miller, and Day, *J. Amer. Chem. Soc.*, 1948, **70**, 1946; 1949, **71**, 1245).

The reactions proceed equally readily with internal esters, *i.e.*, lactones, and acid anhydrides as in the assay of the penicillins (Baker, Dobson, and Martin, *Analyst*, 1950, **72**, 651; Albans and Baker, *ibid.*, p. 657).

It has now been shown that in the carbohydrate series 3 : 6-, 1 : 4-, and 1 : 5-lactones behave in the same way as simple esters and may be determined in the presence of the parent hydroxy-acid. The behaviour of uronic (3 : 6-)lactones is of particular interest because of the frequent occurrence of uronic acids in numerous plant and animal polysaccharides and the possibility of the existence of internal or external lactone bridges in these macro-molecules.

In a preliminary survey absorption spectra were observed for pure acethydroxamic acid reacting with ferric chloride at various acidities. A single absorption peak was found at 5050 Å, where a linear relation existed between extinction and concentration (0—10 μmoles). The colour was stable for 10 minutes and independent of the presence of excess of hydroxylamine. Whilst the intensity increased very slightly with increase in pH to a maximum value at pH 1·7 in the case of acethydroxamic acid (formed *in situ* from ethyl acetate and hydroxylamine and treated with ferric chloride under the same conditions), at 5050 Å it decreased when the pH value fell below 1·0; at lower pH's the intensity at lower wavelengths increased. Accordingly, a final pH value between 1·0 and 1·2 was adopted for later experiments. Otherwise, the results agreed closely with those obtained with preformed acethydroxamic acid. At pH 1·2 a linear relation was found between the extinction and the amount of ethyl acetate (0—10 μmoles). Acetamide reacted only slowly with hydroxylamine, being detectable, under the prescribed conditions, only in comparatively high concentration. Acetic anhydride reacted readily with two mols. of hydroxylamine. In most cases indications were found of a second absorption band at about 4100 Å but it was not possible to use it for quantitative work.

D-Glucurone gave absorption curves with a maximum at 4750 instead of 5050 Å. This was thought to be due to interference from the reducing group. D-Glucose had a maximum at about 4400 Å under similar conditions and correction of the D-glucurone absorption for this superimposed absorption caused maximum to shift from 4750 to 5050 Å. The absorption of D-glucurone was then similar to that of ethyl acetate, and involvement of the lactone ring was demonstrated by failure to detect more than slight absorption at 5050 Å with sodium D-glucuronate. In spite of this superimposed absorption, in the case of D-glucurone the absorption–concentration relation is linear at 5050 Å both before and after correction. Thus, while it is possible to estimate free carbohydrate lactones by this method, in general reducing sugars should be removed or glycosides formed from them. 1 : 4- and 1 : 5-Lactones typified by 2 : 3 : 5- and 2 : 3 : 4-trimethyl L-arabonolactone reacted readily with hydroxylamine, and their estimation could be carried out in the presence of glycosides.

Sugar esters could readily be estimated and as glycosides did not interfere it was possible to determine the total uronic acid content of a polysaccharide (by using the simple uronic ester glycoside as standard) if the material was first esterified; this was most readily accomplished with methanolic hydrogen chloride at 100°. The amount of ester determined in the resulting solutions and the acid values agreed closely with those obtained by titration.

In this way pneumococcus type III polysaccharide gave a value of 54·7% uronic acid components, a value of 50% (acid equivalent 350) being obtained by titration and structural studies (Reeves and Goebel, *J. Biol. Chem.*, 1941, **139**, 511). In the case of pneumococcus type II polysaccharide an acid equivalent of 972 (17·0% uronic acid residues) was found by the present method compared with 1010 determined by titration of identical material. Good agreement has been found in the case of other polysaccharides, *viz.*, hyaluronic acid, alginic acid, etc.

The procedure was applied to dried specimens of polysaccharides to test the possible occurrence of lactone linkages. A virtually ash-free specimen of pneumococcus type II polysaccharide gave no indication of the presence of such linkages even after extensive drying in a vacuum. Pneumococcus type III polysaccharide (ash content 2%), dried at room temperature, was found to contain a small but distinct number of uronic acid residues in the lactone form and this number increased when the polysaccharide was dried at 61°

in a vacuum (1 lactonised unit per 12 uronic acid residues). In the light of the structure proposed by Reeves and Goebel (*loc. cit.*) in which the glucuronic acid residues are linked through positions 1 and 3, the usual 3 : 6-lactone bridge cannot be present and the possibility of an intramolecular lactone being formed in any other way is remote. Probably therefore the lactone bridges in type III polysaccharides are intermolecular. According to Meyer, Fellig, and Fischer (*Helv. Chim. Acta*, 1951, **34**, 939) the glucuronic acid units of hyaluronic acid are also linked in the 1 : 3-positions and this is consistent with the present finding of only small amounts of uronolactone residues in isolated specimens. There is little evidence to support the conjecture of K. Meyer (*J. Biol. Chem.*, 1948, **176**, 993) that uronic anhydrides occur in the native material. It is not known whether the linkages are in fact those of lactones or of anhydrides and the lack of correlation between lactone content and viscosity suggests that if the linkages are intermolecular then they are of minor importance in cross-linkage between chains.

In the case of 1 : 4-linked acidic polysaccharides, *e.g.*, *Rhizobium radicicolum* or alginic acid, the hydroxyl group at $C_{(3)}$ is available for internal lactonisation. *Rhizobium* polysaccharide, dried at room temperature, was found to contain many lactonised residues. According to Schlücterer and Stacey (*J.*, 1945, 776), the material comprises D-glucose and D-glucuronic acid and thus it appears that in the dried material the uronic acid residues are to a large extent lactonised. Similarly, evidence was obtained that dry alginic acid exists chiefly in a lactonised condition. In this case, the extreme insolubility of the material caused difficulties. In general it appears that internal lactonisation (*i.e.*, 3 : 6-) may occur readily when the structure permits.

Experimental

Absorption Spectra of Acethydroxamic Acid–Iron Complex.—(i) *Effect of acid.* Aqueous solutions of acethydroxamic acid (Schroeter, *Ber.*, 1898, **31**, 2191; Jones and Oesper, *Amer. Chem. J.*, 1909, **42**, 518) (m. p. 87°; 10 μmole in 2 ml.) were diluted with water (0·9, 0·8, 0·7, 0·6 ml. severally) and treated with sodium hydroxide (3·5M; 1 ml.) followed immediately by hydrochloric acid (3·34M; 1·1, 1·2, 1·3, 1·4 ml.) and ferric chloride (0·37M in 0·1M-hydrochloric acid; 1 ml.). The final pH's of the solutions were 1·7, 1·2, 1·0, and 0·8 respectively. The absorption spectra were then immediately measured by means of a Beckman spectrophotometer (1-cm. cells). The compensating cell contained respectively, water (2·9, 2·8, 2·7, 2·6 ml.), hydrochloric acid (3·34M; 1·1, 1·2, 1·3, 1·4 ml.), sodium hydroxide (3·5M; 1 ml.), and ferric chloride (1 ml.). (The method used by Hestrin, *loc. cit.*, for preparing a compensating solution by adding the reagents in the reverse order to an aliquot of the solution under test was not found satisfactory.) Results were :

pH value	1·7	1·2	1·0	0·8
Log I/I_0 at 5050 Å	1·145	1·100	1·065	1·030

(ii) *Fading.* At pH 1·2 the extinction of the appropriate foregoing solution was determined at 5050 Å as a function of time :

Time (min.)	0	10	15	35	50	70
Log I/I_0	1·114	1·109	1·102	1·035	1·015	0·994

(iii) *Extinction–concentration relation.* Solutions of pure acethydroxamic acid (10, 7·5, 5·0, 2·5 μmole) in water (2·8 ml.) were treated as in (i) (final pH 1·22) and the extinction was measured within 10 minutes at 5050 Å. :

Acethydroxamic acid (μmole)	10·9	7·5	5·0	2·5
Log I/I_0	1·118	0·801	0·511	0·247

Ultra-violet Absorption of the Iron Complex obtained directly from Ethyl Acetate and Hydroxylamine.—(i) *Effect of acid.* Solutions of ethyl acetate (9 μmole) in 5% aqueous methanol (2 ml.) were diluted with water (1·1, 1·0, 0·9, 0·8 ml. severally) and mixed with a freshly prepared solution of hydroxylamine (2 ml.; from 2M-hydroxylamine hydrochloride and an equal volume of 3·5M-sodium hydroxide). After 4 minutes at room temperature (cf. Hestrin, *loc. cit.*) the solutions were treated with hydrochloric acid (3·34M; 0·9, 1·0, 1·1, 1·2 ml.) and ferric chloride (0·37M in 0·1M-hydrochloric acid; 1 ml.). The final pH values of the solutions were respectively

1·5, 1·2, 1·0, 0·8. Compensating solutions were prepared similarly with 5% aqueous methanol. The resulting solutions were shaken under reduced pressure (15 mm.) for 1 minute to remove dissolved gases, and the extinction was measured as above :

pH	1·5	1·2	1·0	0·9
Log I/I_0	0·843	0·923	0·984	0·952

(ii) *Extinction–concentration relation.* Solutions of ethyl acetate (10·0, 8·1, 7·2, 6·4, 4·5, 4·0, 2·7, 2·4, 1·0 μmole) in 5% aqueous methanol (2 ml.) were treated as above (final pH 1·2), results being :

Ethyl acetate (μmole)	10·0	8·1	7·2	6·4	4·5	4·0	2·7	2·4	1·0
Log I/I_0	1·030	0·855	0·750	0·655	0·460	0·405	0·280	0·250	0·097

Ultra-violet Absorption of Iron Complexes from Various Acetyl Derivatives and Hydroxylamine.—Aqueous solutions (5% aqueous methanol for water-insoluble substances), treated as described in the foregoing paragraph, gave :

Acetic anhydride (μmole)	9·0	7·0	4·0	3·0	1·0
$E_{max.}$ (5050 Å)	1·795	1·393	0·803	0·635	0·215
Acetylcholine chloride (in 0·001N-sodium acetate; cf. Hestrin, *loc. cit.*) (μmole)	5·5	4·1	2·7	1·4	
$E_{max.}$ (5000) Å	0·850	0·645	0·445	0·230	
Acetamide (μmole)	165·0	82·5	50·0	33·3	
$E_{max.}$ (5000 Å)	0·509	0·250	0·160	0·110	

Ultra-violet Absorption of the Iron Complex from D-*Glucurone and Hydroxylamine.*—Aqueous solutions, treated as described above, gave the following results :

μmole	9·2	8·3	7·4	6·9	6·4	5·5	4·6	2·3
Glucurone, E_{4750}	0·982	0·822	0·750	0·710	0·630	0·549	0·475	0·235
,, E_{5050}	0·920	0·780	0·705	0·665	0·585	0·510	0·425	0·205
Glucose, E_{5050}	0·170	0·135	0·125	—	0·105	0·095	—	0·030
Glucurone, E_{5050}, "corr."	0·750	0·645	0·580	—	0·480	0·415	—	0·175

Ultra-violet Absorption of Iron Complexes from Carbohydrate Esters and Lactones with Hydroxylamine.—The following results were similarly obtained :

Dimethyl mucate (μmole)	8·0	6·0	4·0	2·0	1·0
$E_{max.}$ (5050 Å)	1·165	0·900	0·580	0·295	0·198
Methyl methyl-D-galacturonoside (μmole)	10·5	8·4	6·3	2·1	1·05
$E_{max.}$ (5050 Å)	0·850	0·735	0·550	0·205	0·100
*iso*Propylidene D-glucurone (μmole)	9·3	8·36	4·18	1·0	
$E_{max.}$ (5000 Å)	0·950	0·840	0·422	0·104	
2 : 3 : 5-Trimethyl L-arabonolactone (μmole)	10·6	5·3	1·0		
$E_{max.}$ (5050 Å)	1·07	0·489	0·094		
2 : 3 : 4-Trimethyl L-arabonolactone (μmole)	9·73	4·86	2·43	1·0	
$E_{max.}$ (5050 Å)	0·761	0·369	0·179	0·078	
D-Glucono-1 : 4-lactone (μmole)	8·0	6·0	4·0	2·0	1·0
$E_{max.}$ (5050 Å)	0·670	0·570	0·425	0·225	0·075

Total Carboxylic Acid Content of Polysaccharides.—(i) Pneumococcus type III polysaccharide was precipitated by ethanol from an acidic solution. After reprecipitation from aqueous solution it was dialysed in a Cellophane container against distilled water, then was isolated by being freeze-dried. It contained no alkoxyl groups (Zeisel). 1·40 Mg. were heated at 100° with methanolic hydrogen chloride (1%; 0·1 ml.). After 30 minutes the material was added to 1·9 ml. of water and the concentration of ester was measured as described for ethyl acetate. E at 5050 Å = 0·392, equiv. to 4·43 μmole. Total uronic acid content = 55·6; 53·8% in duplicate tests. Authentic D-glucurone, esterified and estimated in this way, gave 98% recovery.

(ii) Pneumococcus type II polysaccharide (1·69 mg.), was treated as above. Extinction at 5050 Å = 0·160, equiv. to 1·80 μmole. Total uronic acid content = 18·7%.

(iii) Hyaluronic acid (N, 2·96; ash, 2·61%) (2·53 mg.) isolated by Kaye's method (*Nature*, 1950, **166**, 478) from umbilical cord and deproteinised by the Sevag technique, was heated at

100° for 1 hour with methanolic hydrogen chloride (0·2 ml.; 1%). The ester content of the resulting solution was determined as before. Extinction at 5050 Å = 550, equiv. to 6·3 μmole. Total carboxylic acid content = 42·7% (cf. 44·9%, Kaye and Stacey, *Biochem. J.*, 1951, **48**, 249).

(iv) Alginic acid (2·07 mg.), reprecipitated in the acidic state and dried at room temperature with ethanol and ether, was heated at 105° for 2 hours with methanolic hydrogen chloride (0·3 ml.; 1%). The ester concentration of the contents was determined by the foregoing method. Extinction at 5050 Å = 0·990, equiv. to 11·2 μmole. Total uronic acid content 94·2% (cf. 100% required by structure of Hirst, Jones, and Jones, *J.*, 1939, 1880).

Lactone Linkages in Dried Acidic Polysaccharides.—(i) *Rhizobium radicicolum* polysaccharide (0·5 g.; $[\alpha]_D^{22}$ −18° in H_2O) was reprecipitated at pH 3 from acetic acid solution by gradual addition of ethanol (5 volumes), and the product was dried by being washed with absolute ethanol (twice), then with ether, and finally in a vacuum over phosphoric oxide at room temperature. The dried material had an ash content of 2·2% and contained no alkoxy-groups (Zeisel). The dried polysaccharide (3·00 mg.) was dissolved in distilled water (2 ml.), and the content of lactonised groups estimated by the foregoing method (*iso*propylidene glucurone as standard). Extinction at 5050 Å = 0·560, equiv. to 5·50 μmole, *i.e.*, 31·2% of the initial polysaccharide is composed of lactonised uronic acid groups. The structure proposed by Schlücterer and Stacey (*loc. cit.*) requires a uronic acid content of 33%; thus most of the uronic acid residues are in the lactone form.

(ii) Pneumococcus type III polysaccharide reprecipitated at pH 3 by ethanol (5 volumes) was dried with absolute ethanol and ether and finally in a vacuum at room temperature. 1·10 Mg. were dissolved in water (2 ml.), and the lactone residues were determined (*iso*propylidene glucurone as standard). Extinction at 5050 Å = 0·013, equiv. to 0·125 μmole, *i.e.*, 2·0% of the initial polysaccharide is composed of uronic acid groups or 4·0% of the total uronic acid groups is lactonised.

The amount of lactone was measured again after a specimen of the same material (1·1 mg.) had been dried at 61° in a vacuum over phosphoric oxide for 1 hour. The extinction value was 0·025, *i.e.*, corresponded to 8·0% lactonisation of the uronic acid residues. This value did not increase when specimens were dried at 61° for longer periods.

(iii) (*a*) A sample of the hyaluronic acid described above and having $\eta_{rel.}$ (at 1 g./l.) of 1·55 for a 0·03% solution was examined for lactone residues. 18·98 Mg. were dissolved in distilled water (2 ml.). The extinction value of the resulting hydroxamic acid–iron complex at 5050 Å was 0·085, equiv. to 1·1 μmole of uronolactone residues, *i.e.*, 2·0% of the acidic residues of the original material in the lactone form (" corrected " glucurone as standard).

(*b*) A sample of hyaluronic acid (pyridine method; precipitate 1) was prepared from umbilical cord by Hadidian and Pirie's procedure (*Biochem. J.*, 1948, **42**, 260). The material contained N, 3·4% (corrected for ash), and ash, 15·2%, and had $\eta_{rel.}$ (at 1 g./l.) of 2·8 for a 0·1% solution and 2·4 for a 0·03% solution. 18·90 Mg. of the polysaccharide, dried at 61° in a vacuum for 1 hour, were dissolved in water (2 ml.) and the amount of lactone was estimated. *E* at 5050 Å = 0·050, equiv. to 1·1% of the uronic acid residues in the lactone form (" corrected " glucurone as standard).

(*c*) Hyaluronic acid (3·26% N, ash, 8·50%; 21·8 mg.), isolated by extraction of umbilical cord with 1% phenol (Kaye, unpublished results) and dried at 61° for 30 minutes in a vacuum, was dissolved in water (2 ml.) and estimated as above. *E* at 5050 Å = 0·180, equiv. to 2·35 μmole of glucurone, *i.e.*, 3·55% of the uronic acid in the lactonised form (" corrected " glucurone as a standard).

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13. *The Thermal Decomposition of the Alumina Trihydrate, Gibbsite.*

By J. F. Brown, D. Clark, and W. W. Elliott.

It has been found that gibbsite can decompose either to the monohydrate, boehmite, or to χ-alumina, which is virtually anhydrous. When the ignition temperature is raised the decompositions of these two primary products follow independent routes but eventually lead to a common product (α-alumina), at 1000°.

The thermal decomposition of the hydrates of alumina to corundum (α-Al_2O_3) has recently been shown by *X*-ray diffraction methods to proceed through a number of intermediate stages. Stumpf, Russell, Newsome, and Tucker (*Ind. Eng. Chem.*, 1950, **42**, 1398) have postulated the existence of six intermediate phases that had previously been collectively termed γ-alumina. Thibon, Tertian, and Charrier (*Bull. Soc. chim.*, 1951, 384) have largely confirmed the observations of Stumpf *et al.* but included in their decomposition scheme a seventh intermediate stage. Whilst undertaking an extensive examination of the physical and chemical properties of alumina hydrates and anhydrous aluminas we have obtained similar results. There are, several respects in which our interpretation differs from that of previous workers but fundamentally there is general agreement that the hydrates of alumina, with the exception of diaspore, decompose initially to poorly crystalline substances, the decompositions of which in turn proceed through a series of intermediate stages to well-crystallised corundum.

The thermal decomposition of the trihydrate, gibbsite, is more complex than that of the other three hydrates, bayerite, boehmite, and diaspore. Since our findings agree fully with those of previous workers for the latter hydrates, we shall confine our attention to gibbsite. The nomenclature adopted here is that proposed by Stumpf *et al.*, and we agree with their definitions of the diffraction patterns of the anhydrous modifications, with the possible exception of that of χ-alumina. We do not, however, propose to distinguish in this paper between γ- and η-alumina since the diffraction patterns of the two modifications are very similar and in many specimens any distinction would be quite arbitrary.

Experimental

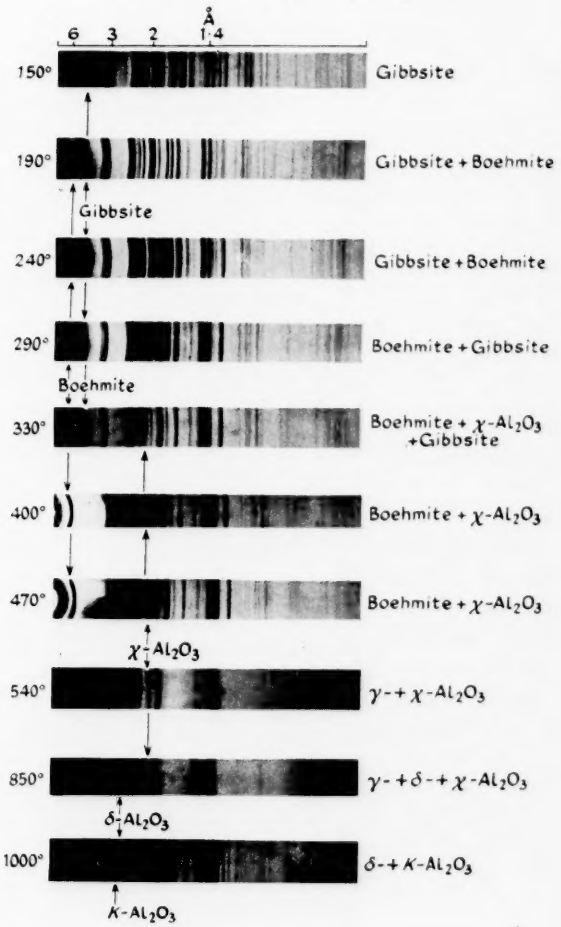
The gibbsite used was prepared by the Bayer process, and contained 0·11% of Na_2O, 0·01% of Fe_2O_3, 0·21% of SO_3, and 34·7% of H_2O. *X*-ray powder diffraction patterns were obtained with Cu-K_α radiation, either 9 or 19 cm. diameter cameras being used. The gibbsite was decomposed thermally in contact with air either by igniting an individual sample to progressively higher temperatures at 40° intervals, retaining each temperature for 1 hour, or by igniting a fresh sample directly to a given temperature which was then maintained for 16 hours.

The diffraction patterns, reproduced in the Plate, were obtained by the former method. Gibbsite was undecomposed below *ca.* 190° but between 200° and 300° it slowly decomposed to boehmite until at 300° the two hydrates were present in approximately equal amounts. At 330° the residual gibbsite suddenly decomposed to χ-alumina, giving a mixture of χ-alumina and boehmite. No further change occurred over the temperature range 330—530°, the ratio χ-alumina : boehmite remaining unchanged. At 530° the boehmite suddenly decomposed to γ-alumina; the sample then consisted of a mixture of χ- and γ-alumina. No further change occurred below 800°, the ratio χ-alumina : γ-alumina remaining constant. Between 800° and 1000° the diffraction patterns became more complex and are best accounted for as those of mixtures of κ- and δ-alumina.

Similar results were obtained by using fresh samples ignited to a single temperature, except that at 550—800° the ratio χ-alumina : γ-alumina decreased with increasing ignition temperature.

These results are taken to indicate that gibbsite decomposes by two mechanisms, *i.e.* (i) to χ-alumina and (ii) to boehmite, which subsequently decomposes to γ-alumina. By using a constant sample the ratios χ-alumina : boehmite and subsequently χ-alumina : γ-alumina are

Progressive heating of a sample of gibbsite.



[*To face p.* 81.

fixed after the disappearance of gibbsite, but the use of a fresh sample for each ignition allows the relative amounts of χ- and γ-alumina to vary with the ignition conditions.

When gibbsite was ignited rapidly on an electrically heated foil in a vacuum, χ-alumina was never formed but boehmite or γ-alumina was formed depending upon the temperature reached. Further, boehmite prepared by vacuum ignition of gibbsite, on subsequent ignition at 550° in air, decomposed to γ-alumina without the formation of χ-alumina.

In general, on ignition at 1000°, mixtures of γ- and χ-alumina rich in the latter gave predominantly κ-alumina whilst mixtures rich in γ-alumina gave predominantly δ- and subsequently θ-alumina. Both κ-rich and θ-rich mixtures appeared to decompose directly to α-alumina; thus when κ-rich mixtures were heated at 1000° for prolonged periods, α-alumina

FIG. 1.

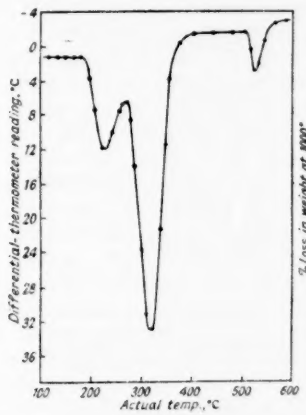
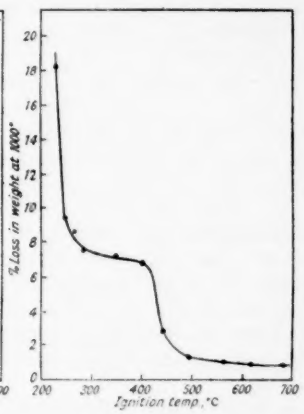
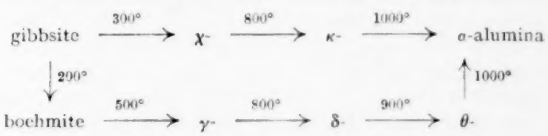


FIG. 2.



was slowly formed without any increase in the trace of the θ-form nor did θ-rich mixtures show an increase in the κ-modification present.

The decomposition of gibbsite may thus be represented by the scheme :



The temperatures shown must be considered indicative only since they depend on heating conditions. Thus prolonged heating in air at 200° does not entirely convert gibbsite into boehmite since χ-alumina is still formed after substantial amounts of gibbsite have decomposed. It is not thought that the impurities in the gibbsite control the formation of the χ-modification, since bayerite or boehmite containing similar impurities does not yield it on thermal decomposition.

Differential thermal analysis of gibbsite in an apparatus similar to that described by Voorthüysen and Franzen (*Rec. Trav. chim.*, 1951, **70**, 793) leads to a curve (Fig. 1) exhibiting three peaks below 550°. This curve is further evidence that gibbsite decomposes by two mechanisms. Thus the first peak is due to the change gibbsite $\longrightarrow$ boehmite, the second to gibbsite $\longrightarrow$ χ-alumina, and the third to boehmite $\longrightarrow$ γ-alumina.

Tran-Huu-The and Prettre (*Compt. rend.*, 1952, **234**, 1366) carried out a similar analysis on gibbsite. They did not resolve the low-temperature peaks into two components nor did they record the peak at 550°, resulting from the decomposition of boehmite. They attached considerable importance to the fact that the zero point after the gibbsite deflections was different from the initial zero point, but their view that the change in zero point is due to the exothermic decomposition of boehmite is untenable because of the subsequent peak at 550°. The relatively small variation in zero points could be accounted for by the change in physical properties accompanying the decomposition of gibbsite to χ-alumina + boehmite.

The water content–ignition temperature curve for gibbsite is shown in Fig. 2. This curve

was obtained by igniting fresh samples of gibbsite to various temperatures and determining the subsequent loss in weight on ignition to 1000° for 4 hours. It is seen there is no break corresponding to the formation of boehmite (15% of H_2O), but there is a break at *ca.* 6% of H_2O; this break corresponds to the fixed ratio of boehmite to χ-alumina in the range 300—400° to which we have previously referred.

The significance of the *ca.* 1% of water that remains on ignition to 500—700° is discussed by De Boer and Houben (Gothenburg Conference on Chemistry of Solids, 1952). They suggest that the water is constitutional and that γ-alumina has a pseudo-spinel structure, HAl_5O_8.

The interplanar spacings of the intermediate anhydrous modifications are tabulated below.

κ	χ	θ	δ	γ	η
6·0 w					
		5·4 w			
5·02 wvv			5·0 mw		
4·45 w	4·5 wb	4·5 mw	4·5 wb	4·5 wb	4·5 wb
4·15 vw			4·05 vw		
3·80 vvw					
		3·54 w	3·54 w		
3·33 vvw		3·32 vw	3·32 vvw		
3·06 m		3·04 vvw			
		2·86 s	2·86 mw		
2·81 ms					
				2·77 vwb	2·77 vwb
2·73 vw		2·73 s	2·73 ms		
			2·59 mw		
2·57 s		2·57 w			
		2·44 s	2·44 ms		
2·43 m				2·41 mb	2·40 mb
2·33 m		2·32 ms			
			2·28 ms	2·28 m	2·29 wb
2·26 vvw		2·26 ms			
2·18 vvw		2·17?	2·19 vvw	2·20 vvw	
2·12 s	2·13 mvb	2·11 vvw		2·09?	
2·06 mw					
		2·02 ms			
1·99 m		1·99 vvw	1·99 s	1·98 msb	1·98 msb
1·95 w		1·95 w	1·94 m	1·95 m	
		1·91 mw			
1·87 m	1·87 vvw				
1·83 mw					
		1·80 w	1·80 w		
		1·78 w			
1·75 w					
		1·74 ww			
1·71 vw	1·71 vvw	1·71?			
1·64 m					
1·61 vvw		1·62 w	1·61 vw		
		1·57 vw			
1·545 vvw		1·54 m.	1·54 mw	1·53 mwb	1·53 vwb
		1·51 vw	1·51 mw		
1·490 mw		1·49 mw			
1·450 mw		1·45 m			
1·435 s		1·43 vw			
	1·40 sb	1·40 m	1·40 m	1·40 m	1·40 msb
1·392 vs		1·39 s	1·39 s	1·39 s	

s = strong. m = moderate. w = weak. v = very. b = broad.

Discussion

There are three independent indications that the trihydrate gibbsite decomposes by two routes, either to the monohydrate boehmite, or directly to the virtually anhydrous χ-alumina. First, the *X*-ray diffraction patterns show that the formation of χ-alumina is coincident with the disappearance of gibbsite and subsequently the amount of the χ-modification does not increase. If boehmite decomposed to χ-alumina it would be expected that the ratio χ-alumina : boehmite would increase with increasing temperature in the range 300—400°. Secondly, differential thermal analysis indicates a thermal arrest in the region 200—300° which may be resolved into two components, neither of which is the decomposition of boehmite to γ-alumina, which occurs at *ca.* 550°. Although only

two hydrates are known to exist in the ignition sequence, three deflections are observed; therefore, one of the hydrates must be decomposing by a dual mechanism. Thirdly, the water content–ignition temperature curve exhibits an arrest in the region 300—400° corresponding very approximately to a hemihydrate. Since there are no independent indication of the existence of an alumina hemihydrate it is reasonable to associate this arrest with a constant ratio of the monohydrate to the virtually anhydrous χ-alumina.

We do not fully understand the factors controlling the degree to which gibbsite decomposes to χ-alumina or to boehmite. Therefore we shall only record that the following ignition conditions increase the degree to which gibbsite yields boehmite or boehmite-decomposition products: (*a*) autoclaving it with water at *ca.* 200°; (*b*) ignition in a vacuum, (*c*) direct ignition in air to about 750° rather than to about 500°.

We have not been able to prepare pure χ-alumina since the decomposition of gibbsite yields χ-alumina + boehmite followed by χ- + γ-alumina. The unique *X*-ray diffraction spacings of the χ-modification must therefore be deduced by subtraction of boehmite or of γ-alumina spacings from the diffraction patterns of the appropriate mixtures. Thus we believe that the diffraction pattern of the χ-form is substantially 2·13 m, 1·87 vvw, 1·40 s.

When gibbsite has completely decomposed to χ-alumina + boehmite, the two components of the mixture follow their own decomposition routes and we have found no evidence of cross linking of the two routes. We have been unable to observe any of the transitions, boehmite $\rightleftharpoons$ χ-, χ- $\rightleftharpoons$ γ-, δ- $\rightleftharpoons$ κ-, θ- $\rightleftharpoons$ κ-alumina.

It follows from the dual decomposition of gibbsite that κ-alumina as defined above and by Stumpf *et al.* and Thibon *et al.* may contain δ- or θ-alumina. A close examination of several preparations of κ-alumina shows small variations of intensity in certain diffraction spacings which are more especially associated with δ- and θ-alumina. There can be no doubt, however, of the existence of two well-crystallised modifications, κ- and θ-, which represent the final states of the two decomposition routes before the formation of the common end product, α-alumina.

Our scheme for the decomposition of gibbsite thus differs from that proposed by Stumpf *et al.* It is not necessary to postulate (cf. Stumpf *et al.*) that boehmite may decompose to either χ- or γ-alumina or that formation of the γ-form may precede the formation of either δ- or κ-alumina. The scheme proposed by Stumpf *et al.* does not account for (i) the constant ratio of χ-alumina to boehmite and of χ- to γ-alumina obtained on ignition of an individual sample, or for (ii) the differential thermal analysis curve.

Thibon *et al.* (*loc. cit.*) proposed a more complex scheme in which the ignition of an individual sample produces κ^1-alumina (which passes through κ- to α-alumina), whilst ignition of a fresh sample produces χ- followed by η-, and thence through θ- to α-alumina. We believe that κ^1-alumina is a mixture of χ- and η-(or γ-)alumina for two reasons. Firstly, the proposed diffraction pattern of κ^1-alumina does not account for the fact that all of the diffuse reflections obtained in the region 500—750° (so-called κ^1-form) are not apparent in the region 300—400° (so-called κ^1-form + boehmite). Secondly, the conclusion that fresh samples alone give χ- + η-(or γ-)alumina appears to be an arbitrary interpretation that is required by the fact that the ratio χ- to γ-alumina varies in the 500—700° region only when a fresh sample is used for each ignition.

The decomposition routes of the four hydrates of alumina may be summarised as follows:

Boehmite decomposes to γ- or to η-alumina, depending on the crystallinity of the monohydrate and the η-form may be regarded as an extremely poorly crystalline γ-alumina.

The precise physical significance of the six modifications of alumina that precede the formation of corundum is at present obscure. It is, however, doubtful whether η-, γ-, or

δ-modifications should be considered to be well-defined phases. No sharp changes can be observed in the powder patterns of the η-, γ-, δ-, or θ-forms which suggests that the transitions are continuous and represent a gradual ordering of the structure by diffusion of Al^{3+} and possibly O^{2-}. θ-Alumina represents the final, completely ordered member of this sequence and is a definite crystallographic structure, as yet undetermined. Similarly χ-alumina may be considered as the precursor of the well-defined κ-alumina.

The authors thank Mr. A. Jenkins for his assistance with the *X*-ray work and Dr. R. J. Young for helpful discussion.

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14. *Binary and Ternary Mechanisms in the Iodination of Acetone.*

By R. P. BELL and P. JONES.

Measurements are reported on the rate of iodination of acetone at 25° in trimethylacetate, acetate, and glycollate buffers at a constant ionic strength of 0·2. The results confirm Dawson and Spivey's finding (*J.*, 1930, 2180) that the expression for the reaction velocity contains a small term involving the product of the concentrations of acid and anion. It is concluded that this term probably results from the production of enol by a ternary mechanism, but that its occurrence does not make it possible to decide whether or not the main reaction takes place by such a mechanism. Some general consequences of the ternary scheme are examined in the light of available experimental evidence, and it is concluded that the ternary mechanism is not of major importance in reactions catalysed by acids and bases in aqueous solution.

SWAIN (*J. Amer. Chem. Soc.*, 1950, **72**, 4578) has recently revived the suggestion originally put forward by Lowry and Faulkner (*J.*, 1925, 2883) that reactions catalysed by acids and bases normally occur by a ternary mechanism, involving simultaneous attack on the substrate by an acid and a base. One of the chief pieces of evidence produced in support of this view is Dawson and Spivey's finding (*J.*, 1930, 2180) that the expression for the rate of iodination of acetone in acetate buffers contains a small product term of the form k_P[HOAc][OAc^-]. Their data certainly require such a term, but it might be objected that they refer to solutions containing high and variable concentrations of electrolyte (>0·75N). It seemed desirable to repeat these measurements at constant and lower ionic strength, especially as recent work on the rate of hydration of acetaldehyde (Bell and Clunie, *Proc. Roy Soc.*, 1952, *A*, **212**, 33) has failed to detect a product term under conditions where it should be prominent according to Swain's treatment. Such measurements are now reported, together with some general considerations about the occurrence and detection of ternary mechanisms.

EXPERIMENTAL

Acetone was purified *via* the sodium iodide compound. Its concentration in the reaction mixtures was always 0·272M, the same as that used by Dawson and his collaborators. All solutions were made up with conductivity water. Acetate buffer solutions were made up from "AnalaR" acetic acid (99·8% pure by titration) and sodium hydroxide solution standardized against constant-boiling hydrochloric acid. Iodine was kept as a M/50-solution in M/4-potassium iodide, and its initial concentration in the reaction mixtures was 0·002M. The total ionic strength of the reaction mixture was made up to $I = 0·2$ by adding sodium chloride.

The reactions were carried out at 25° ± 0·02° and were followed by extracting 10-ml. samples at intervals, and titrating them with 0·01N-thiosulphate (standardized with potassium iodate), starch being used as indicator. Plots of titre against time were strictly linear throughout, and the reaction velocities were calculated from the slopes of these plots.

Results.—The results obtained are given in Tables 1 and 2. The anion concentrations represent mean values, corrected for the small quantity of acid produced during the reaction; *r*

is the stoicheiometric buffer ratio [HA]/[A⁻]. The reaction velocities v are all expressed in moles of iodine per l. per min., referred to unit concentration of acetone. The velocity v'

TABLE 1. *Iodination of acetone in acetate buffers.*

$r = 1{\cdot}00$, $10^5v' = 9{\cdot}7$.

100[OAc⁻]	2·45	2·59	4·89	5·74	7·54	8·69	10·19	13·10	17·50
10^5v, obs.	60·9	63·0	114	132	169	204	234	306	423
,, calc.	60·2	63·0	113	132	173	200	236	308	424

$r = 2{\cdot}00$, $10^5v' = 16{\cdot}5$.

100[OAc⁻]	2·06	4·98	7·41	10·65	13·68	16·60
10^5v, obs.	70·5	152	231	337	442	547
,, calc.	70·0	152	225	332	437	546

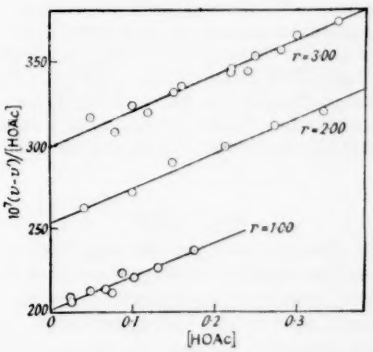
$r = 3{\cdot}00$, $10^5v' = 23{\cdot}4$.

100[OAc⁻]	1·59	2·60	3·29	3·95	4·99	5·31	6·66	6·67	8·01	8·37	9·36	10·03	11·74
10^5v, obs.	73·7	103	130	150	189	201	252	254	299	319	358	393	462
,, calc.	72·9	106	129	152	189	201	251	252	304	318	359	389	462

represents the contribution due to catalysis by H_2O, H_3O^+, and OH^-. It is calculated from the expression

$$v' = v_0 + k_{H_3O^+}[H_3O^+] + k_{OH^-}[OH^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Bell and Lidwell's values of the catalytic constants (*Proc. Roy. Soc.*, **1940**, *A*, **176**, 88) being used, and the activity coefficients of all univalent ions being taken as $f_1 = 0{\cdot}70$ in calculating the



values of $[H_3O^+]$ and $[OH^-]$. Since v' is in most solutions only a small fraction of the total velocity, it is not necessary to know it accurately: in particular the uncertain contribution of OH^- is very small throughout.

The general expression for the reaction velocity can be written in the form

$$v - v' = k_A[HOAc] + k_B[OAc^-] + k_P[HOAc][OAc^-] = [OAc^-]\{k_Ar + k_B + k_P[HOAc]\} \quad (2)$$

It is immediately obvious from the data in Table 1 that the term involving k_P is appreciable, since, if $v - v'$ is plotted against $[OAc^-]$, the data for any one buffer ratio give a line which is markedly convex to the concentration axis: moreover, the velocities observed at higher concentrations are considerably higher than those calculated from the catalytic constants derived by Bell and Lidwell (*loc. cit.*) from measurements at lower concentrations. The validity of equation (2) can be tested by plotting $(v - v')/[OAc^-]$ against [HOAc], which should give parallel straight lines for each buffer ratio of common slope k_P. The figure shows that this expectation is fulfilled within experimental error.

The best values of k_A, k_B, and k_P were obtained, together with their probable errors, by treating the experimental data statistically, assuming that all the experimental errors are in $v - v'$. The results are given in Table 2 (together with earlier values for comparison), and the values of v, calc., in Table 1 are calculated from equations (1) and (2) by use of our values of the constants. The agreement with experiment is excellent, but no such agreement would be obtained if the product term were omitted: the same point is established by the relatively

small probable error in the value of k_P. Our values of k_A and k_B agree reasonably with those of earlier workers, but our value of k_P is considerably greater than that obtained by Dawson and Spivey. This is presumably because they used high and variable salt concentrations (>0·75N), while our experiments refer to a constant ionic strength of $I = 0{\cdot}2$. The contribution of the product term would have been barely detectable in the work of Bell and Lidwell, since the catalyst concentrations were much lower than in the present work.

TABLE 2. *Iodination of acetone in acetate buffers.*

	Present work	Bell and Lidwell	Dawson and Spivey
10^6k_A	5·02 ± 0·09	6·1	4·8
10^6k_B	15·1 ± 0·2	14·7	12·1
10^6k_P	20·4 ± 0·9	—	12·9

It might be suggested that the existence of an appreciable product term depended upon some particular property of acetate buffers, and a few experiments were therefore carried out with buffer solutions prepared from trimethylacetic acid or glycollic acid, the results being given in Table 3. For the former the values of v, calc., are obtained by putting $10k^6_A = 4{\cdot}4$, $10^6k_B = 25$,

TABLE 3. *Iodination of acetone in trimethylacetate and glycollate buffers.*

Trimethylacetate: $r = 0{\cdot}644$, $10^3v' = 6{\cdot}2$.						Glycollate: $r = 0{\cdot}201$, $10^3v' = 14{\cdot}9$.		
$100[CMe_3{\cdot}CO{\cdot}O^-]$ ...	1·66	3·43	5·19	6·96	8·13	$100[CH_2(OH){\cdot}CO{\cdot}O^-]$ ...	12·1	17·2
10^3v, obs.	52·0	103	156	211	250	10^3v, obs.	91	130
,, calc.	52·4	104	156	211	248			

$10^6k_P = 46$. Although there are not sufficient data to warrant the calculation of probable errors, the agreement with experiment shows that a product term of similar magnitude is also present in this catalyst system. The values of k_A and k_B are in reasonable agreement with those obtained by Bell and Lidwell in more dilute solutions. There are only two measured velocities for glycollate buffers, but these are 2% and 7% higher than those calculated from Bell and Lidwell's catalytic constants. This corresponds to a value of k_P of 7—14 × 10^{-6}, and we can therefore conclude that the occurrence of a product term is a general phenomenon in this reaction.

DISCUSSION

The above data confirm the presence of an appreciable cross term of the form $k_P[HA][A^-]$ in the acetone–iodine reaction, and we must now consider whether this means that the whole of the observed reaction takes place by a ternary mechanism, as was concluded by Swain (*loc. cit.*) from Dawson and Spivey's results. Swain makes the reasonable assumption that, if the mechanism is a ternary one, the reaction velocity in a buffer solution can be expressed approximately in the form

$$v = C\{[H_2O] + a_1[HA] + a_2[H^+]\}\{[H_2O] + b_1[A^-] + b_2[OH^-]\} \quad . \quad . \quad (3)$$

Comparing this with equation (1) and (2), we find

$$\left.\begin{aligned} v_0/C &= [H_2O]^2 + a_2b_2K_w & k_A/C &= a_1[H_2O] + a_2b_1K_A \\ k_{H^+}/C &= a_2[H_2O] & k_B/C &= b_1[H_2O] + a_1b_2K_w/K_A \\ k_{OH^-}/C &= b_2[H_2O] & k_P/C &= a_1b_1 \end{aligned}\right\} \quad . \quad (4)$$

where K_w and K_A are the values of the ionic product of water and of the dissociation constant of HA in the solution in question. The expressions for v_0, k_A, and k_B each contain two terms, corresponding to different acid–base pairs. For convenience we shall describe the terms corresponding to H_2O–H_2O, HA–H_2O, and H_2O–A^- as *direct terms*, and those corresponding to H_3O^+–OH^-, H_3O^+–A^-, and HA–OH^- as *indirect terms*.

Swain showed that it is possible to choose values of C, a_1, b_1, a_2, and b_2 which when inserted in equation (4) will reproduce Dawson and Spivey's observed catalytic constants to within a factor of 2. The same is true for the catalytic constants observed in the present work. We shall take throughout $[H_2O] = 55$, $C = 10^{-11}$, $a_2 = 1{\cdot}2 \times 10^6$, $b_2 = 3{\cdot}0 \times 10^{10}$, $K_w = 1{\cdot}7 \times 10^{-14}$ (the appropriate value for $I = 0{\cdot}2$). For acetic acid, $K_A = 3{\cdot}1 \times 10^{-5}$

at $I = 0{\cdot}2$, and if we then put $a_1 = 1 \times 10^2$, $a_1 = 10^4$, equations (4) yield the following results:

$v_0 = 2{\cdot}5 \times 10^{-8}$ $\quad k_{H^+} = 8{\cdot}3 \times 10^{-4}$ $\quad k_{OH^-} = 17$

$k_A = 7{\cdot}4 \times 10^{-6}$ $\quad k_B = 1{\cdot}1 \times 10^{-5}$ $\quad k_P = 2{\cdot}0 \times 10^{-5}$

These values all agree to within a factor of 2 with experiment (cf. Table 2, and Bell and Lidwell, *loc. cit.*), and a similar agreement can be obtained by treating our data for trimethylacetate and glycollate buffers in the same way. It is tempting to follow Swain in regarding this agreement as compelling evidence that the reaction occurs throughout mainly by a ternary mechanism, but closer examination shows that this argument is illusory. The above numerical values being used, the coefficient a_1 makes only a small contribution to both k_A and k_B, so its value can be adjusted within wide limits to fit the observed value of k_P: in other words, any value of k_P between zero and $\sim 10^{-3}$ could be accommodated in the ternary scheme. We must conclude, therefore, that the magnitude of the observed product term does not provide any quantitative evidence for or against the ternary picture.

The ambiguity just mentioned depends upon the fact that in the present instance the dominant term in k_A is the indirect one $a_2b_1K_A$, while the direct term $b_1[H_2O]$ is dominant in k_B. We shall now examine the general consequences of the dominance of different terms in v_0, k_A, and k_B for any reaction showing general acid–base catalysis in aqueous solution. The various possibilities are as follows:

Dominant term in:

	v_0	k_A	k_B
(i)	Direct $[H_2O]^2$	Direct $a_1[H_2O]$	Direct $b_1[H_2O]$
(ii)	Indirect $a_2b_2K_w$	Indirect $a_2b_1K_A$	Indirect $a_1b_2K_w/K_A$
(iii)	Direct $[H_2O]^2$	Indirect $a_2b_1K_A$	Indirect $a_1b_2K_w/K_A$
(iv)	Indirect $a_2b_2K_w$	Direct $a_1[H_2O]$	Direct $b_1[H_2O]$
(v)	Direct $[H_2O]^2$	Indirect $a_2b_1K_A$	Direct $b_1[H_2O]$
(vi)	Indirect $a_2b_2K_w$	Indirect $a_2b_1K_A$	Direct $b_1[H_2O]$
(vii)	Direct $[H_2O]^2$	Direct $a_1[H_2O]$	Indirect $a_1b_2K_w/K_A$
(viii)	Indirect $a_2b_2K_w$	Direct $a_1[H_2O]$	Indirect $a_1b_2K_w/K_A$

These will now be discussed separately.

(i). This gives $k_P/k_A = b_1/[H_2O] = k_B/v_0$, and $k_P/k_B = a_1/[H_2O] = k_A/v_0$. If general acid–base catalysis is to be readily detectable, both k_A and k_B must be much larger than v_0, and in consequence k_P must be much larger than either k_A or k_B, *i.e.*, the product term should account for a large proportion of the observed velocity even at low catalyst concentrations, which does not correspond with experiment. This is essentially the same argument as was used by Pedersen (*J. Phys. Chem.*, 1934, **38**, 590) to exclude the ternary mechanism in the iodination of acetone. It is not applicable to this reaction (*loc. cit.*) where treatment on the basis of equation (4) shows the direct terms to be dominant throughout, but no product term is detectable experimentally.

(ii). Similarly we find $k_P/k_A = a_1/a_2K_A = k_B/v_0$, $k_P/k_B = b_1K_A/b_2K_w = k_A/v_0$. The argument is the same as for (i), and we should again predict a large contribution from the product term.

(iii) and (iv). Neither of these is possible. Thus for (iii), if $a_2b_1K_A \gg a_1[H_2O]$ and $a_1b_2k_w/K_A \gg b_1[H_2O]$, then $a_2b_2k_w \gg [H_2O]^2$; *i.e.*, the indirect term must also be dominant in v_0. The same argument excludes (iv).

(v) and (vi). For either of these we have $k_A/k_B = a_2K_A/[H_2O]$. Since a_2 is independent of the nature of the buffer system HA–A$^-$, this means that for different buffers k_A/k_B is proportional to K_A. If the observed catalytic constants obey the well-known relations $k_A = G_AK_A^\alpha$, $k_B = G_B(1/K_A)^\beta$, this implies that $\alpha + \beta = 1$. The iodination of acetone falls into category (v), and experiment gives $\alpha = 0{\cdot}62$, $\beta = 0{\cdot}88$ (Bell, "Acid–Base Catalysis," Oxford, 1941, p. 91; Bell and Lidwell, *loc. cit.*), so the predicted relation is not obeyed. Moreover, data for other reactions lend no support to this relation: thus for the mutarotation of glucose (Brönsted and Guggenheim, *J. Amer. Chem. Soc.*, 1927, **49**, 2554), $\alpha = 0{\cdot}3$, $\beta = 0{\cdot}34$, while for the depolymerization of dihydroxyacetone (Bell and Baughan, *J.*, 1937, 1947), $\alpha = 0{\cdot}38$, $\beta = 0{\cdot}76$.

(vii) and (viii). Both of these give $k_A/k_B = K_A[H_2O]/b_2K_w$, leading again to the prediction $\alpha + \beta = 1$.

To sum up, the above considerations show that if equation (3) is applied to a reaction exhibiting general acid–base catalysis in aqueous solution, it predicts *either* that the product term $k_P[HA][A^-]$ should contribute a large proportion of the observed velocity in dilute buffer solutions, *or* that the relation $\alpha + \beta = 1$ should hold for the exponents of the Brönsted relations. The available experimental evidence contradicts both these predictions, and therefore indicates that a ternary mechanism is not of major importance in aqueous solution. It seems likely, however, that the product term observed in the iodination of acetone does represent a small contribution from a ternary mechanism, since it is too large to be interpreted in terms of a medium effect.

In order to make quite clear the distinction between the ternary mechanism and the usually accepted one involving successive proton-transfer, we shall consider an isomerization HR ⟶ RH catalysed by a single acid–base pair A–B. The ternary mechanism is

$$B + HR + A \longrightarrow A + RH + B \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

and the rate law predicted in the presence of a number of acid–base pairs is $v = \sum_i \sum_j k_{ij}[A_i][B_j]$. It is not necessary to envisage a simultaneous ternary collision, since the same kinetics result from successive steps such as

$$\left.\begin{array}{ll} & B + HR \rightleftharpoons B,HR;\ B,HR + A \longrightarrow A + RH + B \\ or & HR + A \rightleftharpoons HR,A;\ B + HR,A \longrightarrow A + RH + B \end{array}\right\} \quad . \quad . \quad . \quad (6)$$

with the second step rate-determining. On the other hand, the binary mechanism supposes two alternative mechanisms, as follows:

$$\left.\begin{array}{l} \text{(a) } \textit{Acid catalysis:}\ HR + A \rightleftharpoons B + HRH^+ \longrightarrow A + RH \\ \text{(b) } \textit{Base catalysis:}\ B + HR \rightleftharpoons R^- + A \longrightarrow RH + B \end{array}\right\} \quad . \quad . \quad (7)$$

This scheme leads to a rate law of the form $v = \sum_i k_i^A[A_i] + \sum_j k_j^B[B_j]$. The essential kinetic distinction between (5) or (6) on the one hand and (7) on the other does not lie in the number of steps, but in the fact that in (6) the preliminary equilibria involve association of catalyst and substrate, while in (7) there is a proton-transfer to produce two separate species. This is a clear-cut distinction in a dissociating solvent such as water, but it becomes less clear in a solvent of low dielectric constant where there is likely to be association between the ions produced from the substrate and the catalysts (cf. Bell, *Adv. Catalysis*, 1952, **4**, 182). It has recently been shown (Swain and Brown, *J. Amer. Chem. Soc.*, 1952, **74**, 2534) that the mutarotation of tetramethyl glucose in benzene solution shows third-order kinetics in mixtures of acids and bases, but it is not justifiable to deduce from this that similar reactions proceed by a ternary mechanism in aqueous solution, especially as other catalysed reactions show quite different kinetics in hydrocarbon solvents (Bell and Rybicka, *J.*, 1947, 24).

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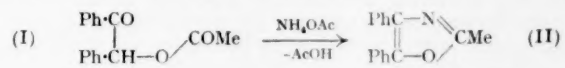
15. *Synthesis of Oxazoles from Ethyl Acetoacetate. Ring-fission of Some Oxazole-5-carboxylic Acids.*

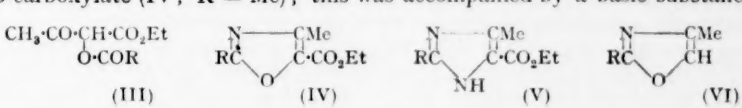
By J. W. Cornforth and Mrs. R. H. Cornforth.

Ethyl 4-methyloxazole-5-carboxylates are obtained by heating ethyl α-chloroacetoacetate with the solution of an ammonium salt in its parent carboxylic acid. Oxazole-4 : 5-dicarboxylic acids, which can be prepared by modifying a known method, undergo ring-fission in boiling water with formation of acylaminopyruvic acids. The latter appear to exist largely in the enolic form, R·CO·NH·CH:C(OH)·CO_2H.

Davidson, Weiss, and Jelling (*J. Org. Chem.*, 1937, **2**, 319) showed that 2-methyl-4 : 5-diphenyloxazole (II) is formed when benzoin acetate (I) is heated with ammonium acetate in acetic acid. Apart from the related observation that benzoin benzoate affords triphenyloxazole with the same reagent, the synthesis was not further developed. If this method were generally applicable it would be important, for oxazole chemistry suffers in comparison with that of other heterocyclic systems from a scarcity of general methods. Some experiments to define the scope of the synthesis were therefore indicated.



Our first attempts were directed to the conversion of acetoxyacetone, CH_3·CO·CH_2·OAc, into 2 : 4-dimethyloxazole. Neither ammonium acetate–acetic acid nor any of the alternative sources of ammonia which were tried proved effective. We turned then to α-acyloxy-β-keto-esters, on the supposition that a readily enolized carbonyl group (which is certainly present in the benzoin esters) might be requisite for oxazole ring formation. Ethyl α-acetoxyacetoacetate (III; R = Me), easily accessible from acetoacetic ester and lead tetra-acetate (Dimroth and Schweizer, *Ber.*, 1923, **56**, 1380), was heated with ammonium acetate in acetic acid. The principal product was the expected ethyl 2 : 4-dimethyloxazole-5-carboxylate (IV; R = Me); this was accompanied by a basic substance which



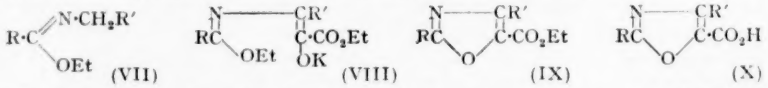
analysis showed to be the corresponding glyoxaline (V; R = Me). To explain the formation of (V) it seems necessary to assume an O ⟶ N acyl migration, thus: CH_3·CO·CH(OAc)·CO_2Et $\xrightarrow{NH_3}$ CH_3·C(NH_2):C(OAc)·CO_2Et ⟶ CH_3·CH(NHAc)·CO·CO_2Et $\xrightarrow{NH_3}$ (V). The possibility had also to be considered of an O ⟶ O acyl migration before closure of the oxazole ring. The orientation of substituents in (IV; R = Me) was therefore proved by hydrolysis to the corresponding acid and decarboxylation. The resulting 2 : 4-dimethyloxazole (VI; R = Me) was identified with a specimen prepared from acetamide and chloroacetone (Oesterreich, *Ber.*, 1897, **30**, 2254). This degradation indicated also that oxazole-5-carboxylic acids, like the 4-isomers, are easily decarboxylated.

The cited preparation of ethyl α-acetoxyacetoacetate being rather a special case, we examined a potentially more general method, the conversion of α-halogenoacetoacetates into the α-acyloxy-analogues (III). Ethyl α-chloroacetoacetate (which was found superior to the α-bromo-ester for this purpose) with sodium phenylacetate suspended in hot toluene gave impure ethyl α-phenylacetoxyacetoacetate (III; R = Ph·CH_2) in moderate yield, and this product with ammonium acetate in acetic acid afforded ethyl 2-benzyl-4-methyloxazole-5-carboxylate (IV; R = Ph·CH_2) along with a minor amount of the glyoxaline (V; R = Ph·CH_2). The overall yield of oxazole was poor; however, a combination of these two stages by heating the chloro-ester with ammonium phenylacetate in phenylacetic acid was more successful, the oxazole (IV; R = Ph·CH_2) being formed directly in

30% yield. Hydrolysis to the 5-carboxylic acid and decarboxylation to 2-benzyl-4-methyloxazole (VI; R = Ph·CH_2) were effected without trouble.

The above composite process evidently proceeds by the stages: (*a*) replacement of halogen by the acyloxy-group; (*b*) reaction of the carbonyl group with ammonia; and (*c*) ring closure; (*a*) and (*b*) need not occur in that order. However, the condensation of amides with α-halogeno-ketones is a known oxazole synthesis, and amides might well be formed under these conditions. To test this alternative ethyl α-chloroacetoacetate was heated in acetic acid with (i) ammonium acetate and (ii) acetamide. The ammonium salt gave the oxazole (IV; R = Me); the amide gave none.

The synthesis was next applied to prepare the hitherto unknown 4-methyloxazole. Ethyl α-chloroacetoacetate was condensed with ammonium formate in formic acid, and the partly purified product [after separation from a little ethyl 4-methylglyoxaline-5-carboxylate (V; R = H)] was hydrolysed to 4-methyloxazole-5-carboxylic acid. This acid was smoothly decarboxylated to 4-methyloxazole (VI; R = H) which is thus available in four stages from ethyl acetoacetate, the overall yield being about 15%.



A previously reported synthesis of oxazole-4-carboxylic esters (*J.*, 1947, 96) and 4-cyano-oxazoles (*J.*, 1948, 1969) involves at one stage the reaction of a (1-alkoxyalkylidene)-aminoacetic acid derivative (VII; R′ = CO_2Et or CN) with ethyl formate–potassium ethoxide. It is shown here that ethyl oxalate may be substituted for ethyl formate, and that the resulting potassium enolates (VIII) undergo the usual ring closure in boiling acetic acid to give oxazole-5-carboxylic esters (IX). This procedure, applied to ethyl 1-ethoxyethylideneaminoacetate (VII; R = Me, R′ = CO_2Et), gave ethyl 2-methyloxazole-4 : 5-dicarboxylate (IX; R = Me, R′ = CO_2Et). The ester was hydrolysed smoothly by alkali, but the resulting 2-methyloxazole-4 : 5-dicarboxylic acid (X; R = Me, R′ = CO_2H) proved difficult to isolate from its salts. The difficulty was traced to a remarkable instability of the free acid; on boiling it with water, formation of a different acid was complete in a few minutes. Analysis of the new acid showed that addition of water and loss of carbon dioxide had taken place. Since the acid gave a deep blue colour with ferric chloride it was evidently acetamidopyruvic acid, or rather its enol Ac·NH·CH:C(OH)·CO_2H, for its intense absorption in the ultra-violet indicated that enolization was substantially complete. The alternative possibility, α-acetamidoformylacetic acid Ac·NH·CH(CHO)·CO_2H, is excluded by the relative stability of the acid and the fact that the colour with ferric chloride is blue and not red (cf. "The Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 805, where α-hexanamidoformylacetic acid is described). The related benzamidopyruvic acid, reported to give a blue-green colour with ferric chloride, was prepared by Wislicenus (*Ber.*, 1891, **24**, 1262) by acid hydrolysis of ethyl 2-benzamido-3-keto-succinate.

From 2-benzyloxazole-4 : 5-dicarboxylic acid (X; R = Ph·CH_2, R′ = CO_2H), phenylacetamidopyruvic acid was obtained under similar conditions. On the other hand, 2 : 4-dimethyloxazole-5-carboxylic acid resisted the action of boiling water or dilute acid. The inference that an electron-attracting group in the 4-position is necessary for this ring-fission was supported by the behaviour of 2-benzyl-4-cyano-oxazole-5-carboxylic acid (X; R = Ph·CH_2, R′ = CN); this acid was slowly decomposed by boiling water to a product which, though not obtained pure, gave a blue colour with ferric chloride. Some attempts were made to prepare the aldehydo-acid (X; R = Ph·CH_2, R′ = CHO), or its ester, from the corresponding nitriles, but the Stephen reduction was ineffective and treatment of the thioamides (IX and X; R = Ph·CH_2, R′ = CS·NH_2) with Raney nickel was equally unsuccessful.

Experimental

Experiments with Acetoxyacetone.—Acetoxyacetone was heated with (i) ammonium carbamate at 85—90°, (ii) ammonium oxalate and oxalic acid in boiling acetic acid, and (iii) ammonium acetate in boiling acetic acid. The mixtures were worked up for volatile alkali-stable products. No indication of 2 : 4-dimethyloxazole was found.

Reaction of Ethyl α-Acetoxyacetoacetate with Ammonium Acetate.—Ethyl α-acetoxyacetoacetate (7 g.) and ammonium acetate (13 g.) in acetic acid (33 c.c.) were boiled under reflux for 1¼ hours. Most of the acetic acid was removed at low pressure; the residue was diluted with water, and solid potassium carbonate was gradually added. Precipitation occurred while the solution was still acid. The mixture was chilled in ice, and the solid product (A) collected and dissolved in a little light petroleum. After decantation from a small oily residue the solvent was removed, leaving a crystalline solid (4 g.), m. p. *ca.* 48°. Two recrystallizations from light petroleum (b. p. 40—60°) gave *ethyl* 2 : 4-*dimethyloxazole-5-carboxylate* in colourless needles, m. p. 55—56° (Found: C, 56·5; H, 6·3; N, 7·8. $C_8H_{11}O_3N$ requires C, 56·8; H, 6·5; N, 8·3%). The ester was moderately soluble in water and easily soluble in all other solvents tried. A sample volatilized when kept overnight in a vacuum-desiccator. The filtrate from (A) was made alkaline with potassium carbonate. The precipitated solid (0·75 g.) was recrystallized thrice from benzene (the first time with charcoal). The resulting *ethyl* 2 : 4-*dimethylglyoxaline-5-carboxylate* formed colourless leaflets, m. p. 165—167°, sparingly soluble in warm ether and insoluble in light petroleum (Found: C, 57·5; H, 7·1; N, 16·1. $C_8H_{12}O_2N_2$ requires C, 57·1; H, 7·1; N, 16·6%).

2 : 4-*Dimethyloxazole-5-carboxylic Acid and* 2 : 4-*Dimethyloxazole.*—The crude oxazole ester (4·6 g.) was obtained when a mixture prepared as above was neutralized (without prior removal of acetic acid) with potassium carbonate, and the extract obtained by light petroleum was separated from the insoluble glyoxaline and evaporated at low pressure. 2N-Sodium hydroxide (20 c.c.) was added; after a few minutes' boiling, charcoal was stirred in. The cooled filtered solution was acidified (Congo-red). The crystalline 2 : 4-*dimethyloxazole-5-carboxylic acid* was dried (4 g.); recrystallization from ethanol–ethyl acetate or from much hot water gave needles, m. p. 247° (decomp.) (Found: C, 51·4; H, 4·8; N, 10·0. $C_6H_7O_3N$ requires C, 51·1; H, 5·0; N, 9·9%).

The acid (2 g.) was heated in quinoline (20 c.c.) with a trace of copper oxide, so that the oxazole distilled slowly along with some quinoline. Two redistillations, the second over potassium hydroxide, gave 2 : 4-dimethyloxazole (0·6 g.). The base was characterized as the *picrate*, m. p. 110—111° (softening from 100°), from ethanolic picric acid (Found: C, 40·4; H, 3·0; N, 17·0. $C_5H_7ON,C_6H_3O_7N_3$ requires C, 40·5; H, 3·1; N, 17·2%), and the mercuric chloride *adduct*, prisms, m. p. 147—148°, from ether (Found: C, 15·7; H, 2·2; N, 3·9. $C_5H_7ON,HgCl_2$ requires C, 16·3; H, 2·0; N, 3·8%). This adduct crystallizes from benzene in fine needles melting at 130° to 138° (dependent on rate of heating) to a turbid liquid. The two forms are interconvertible.

2 : 4-Dimethyloxazole was prepared from acetamide and chloroacetone. The picrate and mercuric chloride adduct were identical with the above derivatives.

Reaction of Ethyl α-Chloroacetoacetate with Sodium Phenylacetate.—A mixture of the ester (2·5 g.) and the sodium salt (5 g.) with dry toluene (15 c.c.) was boiled under reflux for 1 hour, cooled, washed with water and aqueous sodium hydrogen carbonate, dried, and distilled. The fraction, b. p. 115—120°/0·05 mm. (1·6 g.), on redistillation had b. p. 104°/0·02 mm. This fraction, an oil, gave a slowly developing deep red colour with ferric chloride in ethanol and contained the desired ethyl α-phenylacetoxyacetoacetate; analyses, however, were erratic. The product was characterized by heating it with phenylhydrazine acetate, whereupon 5-*methyl-2-phenyl-4-phenylacetoxypyrazol-3-one* was obtained in almost colourless prisms after crystallization from ethanol and then from benzene (Found: C, 70·0; H, 5·4. $C_{18}H_{16}O_3N_2$ requires C, 70·1; H, 5·2%).

The use of benzene or ethanol as reaction media, or the substitution of ethyl α-bromoacetoacetate for the α-chloro-ester, gave inferior yields.

Ethyl 2-Benzyl-4-methyloxazole-5-carboxylate.—(i) Crude ethyl α-phenylacetoxyacetoacetate (4·25 g.) was refluxed in acetic acid (20 c.c.) with ammonium acetate (7·4 g.) for 1¼ hours. Water and ether were added to the cooled solution; the ether was washed with water and aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated. The residue was extracted with hot light petroleum (b. p. 60—80°). Removal of the solvent and distillation gave the *oxazole* ester, a colourless oil (2·1 g.), b. p. 112°/0·05 mm. (Found: N, 5·4. $C_{14}H_{15}O_3N$ requires N, 5·7%). From the petroleum-insoluble residue and by neutralization of the aqueous layer from the ether-extraction, a total of 0·5 g. of crystalline solid was recovered. Recrystallization from benzene gave *ethyl 2-benzyl-4-methylglyoxaline-5-carboxylate*, colourless plates, m. p. 167—168° (Found: C, 68·6; H, 6·7; N, 11·7. $C_{14}H_{16}O_2N_2$ requires C, 68·8; H, 6·6; N, 11·5%). The oxazole ester (1·05 g.) was heated with 2N-sodium hydroxide (3 c.c.) and ethanol (1 c.c.) for ½ hour. The cooled diluted solution was acidified. The precipitated 2-*benzyl-4-methyloxazole-*

5-carboxylic acid crystallized from alcohol in prisms (0·8 g.), m. p. 238° (decomp.) with previous softening (Found : C, 66·5; H, 5·2; N, 6·0. $C_{12}H_{11}O_3N$ requires C, 66·4; H, 5·1; N, 6·5%).

(ii) Aqueous ammonia (4·2 c.c.; *d* 0·88) was added to phenylacetic acid (20 g.), and the water removed by heating at low pressure. Ethyl α-chloroacetoacetate (2·5 g.) was added and the mixture heated for 4—5 hours (bath at 130°), initially under reflux at low pressure. The cooled mixture was diluted with water, made alkaline with potassium carbonate, and extracted with light petroleum (60—80°). Distillation gave the oxazole ester (1·15 g.) which was hydrolysed to the acid (0·9 g.).

2-Benzyl-4-methyloxazole.—2-Benzyl-4-methyloxazole-5-carboxylic acid (0·9 g.) was heated to 280—290° (metal-bath) and gave *2-benzyl-4-methyloxazole* (0·6 g.), a colourless oil, b. p. 250° (Found : C, 76·0; H, 7·2; N, 8·6. $C_{11}H_{11}ON$ requires C, 76·0; H, 6·4; N, 8·1%). The mercuric chloride *adduct* crystallized in prisms, m. p. 88°, from ether–light petroleum (Found : N, 3·4. $C_{11}H_{11}ON,HgCl_2$ requires N, 3·2%).

4-Methyloxazole-5-carboxylic Acid.—Ethyl α-chloroacetoacetate (5 g.) was refluxed for 5 hours with ammonium formate (10 g.) in formic acid (30 c.c.). After addition of water the reaction mixture was neutralized with potassium carbonate and extracted with ether. The extract on distillation gave a fraction (2·4 g.), b. p. 90—110°/20 mm., containing unchanged chloro-ester. It was hydrolysed by boiling 2N-sodium hydroxide (10 c.c.) in a few minutes. Acidification gave a crystalline precipitate and a small second crop was obtained by concentrating the filtrate (total yield, 1 g.). On recrystallization from ethyl acetate *4-methyloxazole-5-carboxylic acid* separated in needles, m. p. 237—238° (decomp.) (Found : C, 47·0; H, 4·1. $C_5H_5O_3N$ requires C, 47·2; H, 3·9%). A somewhat lower yield was obtained in several experiments where the reaction time and the quantities taken were varied. In some experiments *ethyl 4-methylglyoxaline-5-carboxylate* was isolated; it remained undissolved on addition of ether to the diluted reaction mixture and was purified by crystallization from ethanol. It formed colourless plates, m. p. 204—205° (Found : C, 54·3; H, 6·2; N, 18·0. $C_7H_{10}O_2N_2$ requires C, 54·5; H, 6·5; N, 18·2%).

4-Methyloxazole.—4-Methyloxazole-5-carboxylic acid (5 g.; not recystallized) was heated in 1-g. portions with a little copper oxide, so that the product (2·65 g.) distilled slowly. Redistillation over solid sodium hydroxide gave *4-methyloxazole* as a mobile liquid, b. p. 88—89°, of strong pyridine-like odour (Found : C, 58·1; H, 6·0; N, 17·4. C_4H_5ON requires C, 57·8; H, 6·0; N, 16·9%). An unstable picrate separated slowly in small amount from aqueous picric acid. A mercuric chloride adduct, prepared in aqueous solution, crystallized from ether–light petroleum in needles changing to prisms, m. p. 122°, which reverted to mercuric chloride on drying *in vacuo*.

Ethyl 2-Methyloxazole-4 : 5-dicarboxylate.—A solution prepared from potassium (2 g.), ethanol (7·5 c.c.), and ether (25 c.c.) was diluted with ether (175 c.c.) and cooled to —5°. A mixture of ethyl 1-ethoxyethylideneaminoacetate (9·05 g.; freshly distilled) and ethyl oxalate (7·8 g.) was added. A crystalline precipitate appeared after about 20 minutes. Next day the fluffy, light yellow, hygroscopic potassium salt (VIII; R = Me, R′ = CO_2Et) was collected (6·6 g.). It had m. p. 86—88° and deteriorated rapidly. Gradual addition of dilute alcoholic ferric chloride to a solution of the salt in alcohol gave a red colour deepening through purple to pure blue and then fading through green to yellow-brown. The salt and the concentrated mother-liquor were added separately to boiling acetic acid; after dilution with water and neutralization with potassium carbonate the products were isolated by means of ether, united, and distilled. *Ethyl 2-methyloxazole-4 : 5-dicarboxylate*, a colourless oil (7·2 g.), was collected at 82—84°/0·04 mm. (Found : C, 52·5; H, 5·8. $C_{10}H_{13}O_5N$ requires C, 52·9; H, 5·7%).

2-Methyloxazole-4 : 5-dicarboxylic Acid and Acetamidopyruvic Acid.—The above ester (1·5 g.) was heated for a few minutes with 2N-sodium hydroxide (7 c.c.). After concentration at low pressure the liquid was cooled in ice during the addition of concentrated hydrochloric acid (2 c.c.). After a few minutes' stirring the crystalline product was collected and washed rapidly with a little ice-water. The dried residue was extracted with hot ethyl acetate; concentration of the extract gave *2-methyloxazole-4 : 5-dicarboxylic acid*, fine colourless needles (0·1 g.), m. p. 178—179·5° (decomp.) (Found, after drying at 80° : C, 41·9; H, 2·6; N, 8·6. $C_6H_5O_5N$ requires C, 42·1; H, 2·9; N, 8·2%). From the aqueous mother-liquors a further quantity (0·6 g.) of slightly less pure material was obtained by evaporation at low pressure, extraction with ethyl acetate, and recrystallization of the evaporated extract from methanol. When less hydrochloric acid was used for acidification the *sodium hydrogen* salt separated in hydrated needles, m. p. (after drying) 268° (decomp.) (Found : N, 7·8. $C_6H_4O_5NNa$ requires N, 7·3%).

When the free acid was boiled with water, or when a solution of the sodium hydrogen salt

was acidified to Congo-red and boiled, carbon dioxide was evolved. Extraction of the solution with much ether and recrystallization of the product from *iso*propanol–ether gave ***acetamidopyruvic acid*** in prisms, m. p. 184—188° (decomp.; dependent on rate of heating) (Found: C, 41·2; H, 5·1. $C_5H_7O_4N$ requires C, 41·4; H, 4·8%). The acid dissolved easily in water to a solution giving a deep blue colour with ferric chloride and showing an ultra-violet absorption maximum at 2700 Å (ε, 17,600) and a minimum at 2250 Å (ε, 2750). The 2 : 4-*dinitrophenylhydrazone* (prepared in cold 2N-hydrochloric acid) separated slowly as orange platelets, m. p. 206° (decomp.), before and after recrystallization from dioxan (Found: C, 40·7; H, 3·3; N, 21·3. $C_{11}H_{11}O_7N_5$ requires C, 40·6; H, 3·4; N, 21·6%).

2-Benzyloxazole-4 : 5-dicarboxylic Acid.—Potassium (1·7 g.) was dissolved in a mixture of ethanol (6·4 c.c.) and ether (30 c.c.). More ether (130 c.c.) was added and the solution cooled to −5°. A mixture of ethyl 1-ethoxy-2-phenylethylideneaminoacetate (10·5 g.) and ethyl oxalate (6·6 g.) was added. After being kept overnight at 0° the ether was removed at low pressure and the residue added to boiling acetic acid (30 c.c.). The product was worked up as usual. Distillation gave a fraction (4·3 g.), b. p. 136—140°/0·01 mm., which gradually deposited some crystals (0·4 g.; m. p. 81—82° after crystallization from benzene–light petroleum; hydrolysed by alkali to an acid, m. p. 142—143°) of unknown nature, which were removed. The filtrate was redistilled and the distillate (3 g.) hydrolysed with alcoholic potassium hydroxide (22 c.c. of N). The crystalline potassium salt was collected and recrystallized twice from methanol–ethanol. The salt (1·35 g.), m. p. 252° (decomp.), was dissolved in water, acidified with hydrochloric acid, and shaken with ethyl acetate until dissolution was complete. The ethyl acetate was dried and concentrated, whereupon crystallization set in. Recrystallization of the product (0·5 g.) from ethyl acetate gave *2-benzyloxazole-4 : 5-dicarboxylic acid* in prisms, m. p. 178° (decomp.) (Found: C, 58·3; H, 3·8; N, 5·4. $C_{12}H_9O_5N$ requires C, 58·3; H, 3·6; N, 5·7%).

Phenylacetamidopyruvic Acid.—The above acid (100 mg.) in water (4 c.c.) and hydrochloric acid (1 drop of 10N) were refluxed for 3 hours. The solid product was collected after cooling and crystallized from butanol: ***phenylacetamidopyruvic acid*** separated in prisms, sparingly soluble in water and most organic solvents (Found: C, 59·6; H, 5·3; N, 6·2. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0; N, 6·3%). It decomposed from 195° and was completely fused at 212°. When covered with aqueous alcoholic ferric chloride the crystals became blue; the reagent became green.

Ethyl 2-Benzyl-4-cyano-oxazole-5-carboxylate and Derivatives.—1-Ethoxy-2-phenylethylideneaminoacetonitrile was prepared from ethyl phenylacetimidate and aminoacetonitrile sulphate essentially as described for the 1-methoxy-analogue (*J.*, 1949, 1549). This technique was found more reliable than the previously described method (*loc. cit.*). The reaction with ethyl oxalate was carried out as described in the previous example; a crystalline potassium salt (VIII; R = Ph·CH_2; R′ = CN) separated in small amount [m. p. 145—147° (decomp.); deep red → dark green → light green with ferric chloride in ethanol] but it was better to evaporate the reaction mixture and to add the total residue to boiling acetic acid. The product was isolated by distillation after the usual extraction procedures; from the nitrile (15·5 g.) was obtained a distillate (12·6 g.; b. p. ~130°/0·05 mm.) which crystallized. Recrystallization from light petroleum (b. p. 60—80°) gave *ethyl 2-benzyl-4-cyano-oxazole-5-carboxylate* in prismatic needles, m. p. 45—46° (Found: C, 65·7; H, 4·9; N, 11·0. $C_{14}H_{12}O_3N_2$ requires C, 65·6; H, 4·7; N, 10·9%).

Hydrogen sulphide was passed for 4 hours through a solution of this product (1 g.) and triethanolamine (0·6 g.) in ethanol (5 c.c.). Next day the orange crystals (0·9 g.; m. p. 132°) were recrystallized from ethanol. *Ethyl 2-benzyl-4-thiocarbamyloxazole-5-carboxylate* (IX; R = Ph·CH_2; R′ = CS·NH_2) separated as orange plates (0·7 g.), m. p. 136—137° (Found: C, 57·9; H, 4·7; N, 9·5. $C_{14}H_{14}O_3N_2S$ requires C, 57·6; H, 4·8; N, 9·7%). In an earlier experiment diethanolamine had been used, but the *bis*-2-*hydroxyethylamide* was then the product (pale yellow prisms, m. p. 104—105°) (Found: C, 55·0; H, 5·3; N, 12·4. $C_{16}H_{19}O_4N_3S$ requires C, 55·0; H, 5·4; N, 12·0%).

2-Benzyl-4-cyano-oxazole-5-carboxylic Acid and Derivatives.—The 4-cyano-ester (1·28 g.) was treated with a slight excess of N-potassium hydroxide in methanol. After 1½ hours the crystalline *potassium* salt of the 5-carboyxlic acid was collected (1·1 g.). A sample after recrystallisation from ethanol formed platelets, decomp. 229—230° (Found: N, 9·6. $C_{12}H_7O_3N_2K,H_2O$ requires N, 9·8%). When this salt (0·5 g.) was dissolved in a little water and acidified (Congo-red), an acid potassium *salt* separated and crystallized from ethanol in plates (0·3 g.), m. p. 204—205° (Found: N, 11·4. $C_{12}H_7O_3N_2K,C_{12}H_8O_3N_2$ requires N, 11·3%). The free *2-benzyl-4-cyano-oxazole-5-carboxylic acid* was obtained by shaking either potassium

salt with ether and an excess of dilute sulphuric acid; the acid recovered from the ethereal layer crystallized from benzene in colourless plates, m. p. 156—157° (softening) (Found: C, 63·1; H, 3·6; N, 12·1. $C_{12}H_8O_3N_2$ requires C, 63·2; H, 3·6; N, 12·3%).

When the cyano-ester was hydrolysed under more vigorous conditions (2N-aqueous alkali at 100° for 1 hour), *2-benzyl-4-carbamyloxazole-5-carboxylic acid* (X; R = Ph·CH_2, R′ = CO·NH_2) was isolated, having m. p. 200—202° after crystallization from ethanol (Found: N, 11·1. $C_{12}H_{10}O_4N_2$ requires N, 11·4%).

The thioamide ester (IX; R = Ph·CH_2, R′ = CS·NH_2) was hydrolysed by dropwise addition of aqueous N-sodium hydroxide to a suspension of the ester (1·45 g.) in ethanol (15 c.c.) containing a little phenolphthalein. When the colour of the indicator was stable for 1 hour the alcohol was removed, and water and dilute hydrochloric acid were added. The precipitated solid was recrystallised from *n*-butanol, giving orange hexagonal prisms (1·06 g.), m. p. 196° (decomp.), of *2-benzyl-4-thiocarbamyloxazole-5-carboxylic acid* (Found: C, 55·2; H, 3·7; N, 10·5. $C_{12}H_{10}O_3N_2S$ requires C, 55·0; H, 3·8; N, 10·7%).

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16. *Wool Wax. Part III.* Synthesis of Some* iso-*Acids.*

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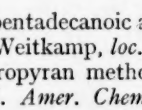
8-Methylnonanoic,† 10-methylundecanoic, 12-methyltridecanoic, 16-methylheptadecanoic, and 18-methylnonadecanoic acids have been synthesised. The melting points and long *X*-ray crystal spacings of the solid acids and amides have been recorded for comparison with those of *iso*-acids from wool wax.

A SERIES of *iso*-acids was required in connection with the branched-chain compounds which exist in both the acid (Weitkamp, *J. Amer. Chem. Soc.*, 1945, **67**, 447) and alcoholic (Murray and Hatt, personal communication) fractions of saponified wool wax. We investigated four modern methods of chain lengthening for convenience of preparation of reasonable quantities of the necessary pure saturated *iso*-compounds. Some of the difficulties encountered since this work was initiated three years ago have been noted by others.

14-Methylpentadecanoic acid was not prepared since it has been satisfactorily identified in wool wax (Weitkamp, *loc. cit.*).

The dihydropyran method (Crombie and Harper, *J.*, 1950, 1707; Brandon, Derfer, and Boord, *J. Amer. Chem. Soc.*, 1950, **72**, 2120) was used with *iso*butylmagnesium bromide, giving *cis*- and *trans*-2-*iso*butyl-3-chlorotetrahydropyran (I), which on ring scission and hydrogenation gave 7-methyloctanol, converted through the bromide and nitrile into 8-methylnonanoic acid (II).



(I)

$Pr^i·[CH_2]_n·CO_2H$

(II; $n = 6$) (V; $n = 14$)
(III; $n = 8$) (VI; $n = 16$)
(IV; $n = 10$)

10-Methylundecanoic acid (III) was prepared from two sets of intermediates by a modification of Bowman's ketone method (*J.*, 1950, 174) in that the acid chlorides (4-methylpentanoylchloride, 2-methylpropanoyl chloride) reacted in the presence of one equivalent of sodium with polymethylene αω-dimalonic esters [benzyl pentane-1 : 1 : 5 : 5-tetracarboxylate (VII), benzyl heptane-1 : 1 : 7 : 7-tetracarboxylate (VIII)] instead of with monomalonic esters. Yields of the keto-acids after debenzylation were poor so that the advantage of using the more readily available dimalonic esters is outweighed by losses probably arising, in part,

* Part II, Rossouw and von Rudloff (*J. Appl. Chem.*, 1952, **2**, 335).
† Geneva nomenclature (CO_2H = 1) is used throughout this paper for naming the *iso*-acids.

from the occurrence of addition of acid chloride to both functional ends of the dimalonic ester molecule; in agreement with Nunn's report (*J.*, 1951, 1740) undesired ketonic hydrolysis of the intermediate β-keto-esters also occurred. A third source of loss in the case of (VII) arose from Dieckmann cyclisation, in the presence of the sodium, detected

$$\mathrm{Pr^i{\cdot}[CH_2]_n{\cdot}COCl} + \underset{\text{(VII; } m = 3\text{)}}{(\mathrm{CH_2Ph{\cdot}O_2C)_2CH{\cdot}[CH_2]_m{\cdot}CH(CO_2{\cdot}CH_2Ph)_2}} \xrightarrow{\mathrm{Na}} \underset{\text{(VIII; } m = 5\text{)}}{}$$

$$\mathrm{Pr^i{\cdot}[CH_2]_n{\cdot}CO{\cdot}C(CO_2{\cdot}CH_2Ph)_2{\cdot}[CH_2]_m{\cdot}CH(CO_2{\cdot}CH_2Ph)_2} \xrightarrow[(2)\ -3CO_2]{(1)\ H_2\text{-catalyst}} \mathrm{Pr^i{\cdot}[CH_2]_n{\cdot}CO{\cdot}[CH_2]_{m+2}{\cdot}CO_2H}$$

by the identification of *cyclo*hexanone at the end of the series of operations; the use of malonic esters is therefore best restricted to those in which the chain is either too long or too short to favour intramolecular cyclisation. The keto-acids obtained after the hydrogenolysis step were smoothly reduced by Huang-Minlon's procedure (*J. Amer. Chem. Soc.*, 1946, **68**, 2487).

12-Methyltridecanoic acid (IV) was prepared by the chloro-iodide–alkylacetylene method of Strong *et al.* (*ibid.*, 1948, **70**, 1699, 3391) starting from 6-methylhept-1-yne and 1-chloro-5-iodopentane:

$$\mathrm{Pr^i{\cdot}[CH_2]_3{\cdot}C{\equiv}CNa} + \mathrm{I{\cdot}[CH_2]_5{\cdot}Cl} \longrightarrow \mathrm{Pr^i{\cdot}[CH_2]_3{\cdot}C{\equiv}C{\cdot}[CH_2]_5{\cdot}Cl} \xrightarrow[(2)\ \mathrm{NaOH}]{(1)\ \mathrm{NaCN}}$$

$$\mathrm{Pr^i{\cdot}[CH_2]_3{\cdot}C{\equiv}C{\cdot}[CH_2]_5{\cdot}CO_2H} \xrightarrow{2H_2} \underset{\text{(IV)}}{\mathrm{Pr^i{\cdot}[CH_2]_{10}{\cdot}CO_2H}}$$

No difficulties were encountered, but attempts to condense 6-methylhept-1-yne with 1-chloro-10-iododecane were abortive. This is analogous to the failure of Taylor and Strong (*ibid.*, 1950, **72**, 4263) to condense alkylacetylenes containing more than nine methylene groups with chloro-iodides. Huber (*ibid.*, 1951, **73**, 2730) has since caused hept-1-yne to react with 1-chloro-10-iododecane, and Lumb and Smith (*Chem. and Ind.*, 1952, 358) have condensed the lithium derivative of *n*-tridec-1-yne with 1-chloro-3-iodopropane so that the limitations noted by Taylor and Strong and by us can be overcome at least in some cases. In practice the use of chloro-iodides is restricted by the difficulty of separating, by fractional distillation, dichloride–chloro-iodide–di-iodide mixtures when the chain is long.

The anodic method of Linstead *et al.* (*J.*, 1950, 3326) was used to synthesise 8-methylnonanoic acid (II) (from 4-methylpentanoic acid and ethyl hydrogen adipate), 10-methylundecanoic acid (III) (from 3-methylbutanoic acid and ethyl hydrogen azelate), 12-methyltridecanoic acid (IV) (from 4-methylpentanoic acid and ethyl hydrogen sebacate), 16-methylheptadecanoic acid (V) (from 12-methyltridecanoic acid and ethyl hydrogen adipate), and 18-methylnonadecanoic acid (VI) (from 10-methylundecanoic acid and ethyl hydrogen sebacate). This method proved the best, for our purpose, because of the ready availability of the starting materials, the reasonable yields obtained, and the smallness of the working losses arising from the fact that it is a one-step synthesis.

In both the Bowman and the Linstead method, it has been advisable to choose the starting materials so that the unwanted dicarboxylic acids arising from ketonic hydrolysis and symmetrical coupling are readily separable by fractional distillation from the desired products. To a lesser extent, dicarboxylic acid by-products also arise in the acetylenic method in cases where the chloro-iodide cannot be fractionated entirely free from di-iodide. It is suggested that, in such cases, the use of Craig's counter-current distribution method (*Ann. N.Y. Acad. Sci.*, 1951, **53**, 1015) is appropriate for purification of the end product since there are large differences in solubility in polar and non-polar solvents between aliphatic monocarboxylic and dicarboxylic acids of similar boiling points. Two examples are in the Experimental.

The properties of the synthetic acids and their amides are compared in the Table with those which Weitkamp (*loc. cit.*) and Velick (*J. Amer. Chem. Soc.*, 1947, **69**, 2317) recorded for wool wax *iso*-acids and with those taken from the compilation in the paper of Ställberg, Stenhagen, *et al.* (*Arkiv Kemi, Min., Geol.*, 1948, **26**, *A*, No. 19). Direct comparison of

our synthetic C_{12} and C_{20} *iso*-acids with specimens isolated by Dr. Weitkamp from wool wax showed that there was no depression of melting points; this and the close comparisons of properties in the Table confirm the validity of Weitkamp's structural assignments.

Acid *	M. p.		Long crystal spacing (Å)	
	Acid	Amide	Acid	Amide
8-Methylnonanoic	23·7—24·0°	103·8°	19·93	19·80 [c]
	Liquid [4]	103·1 [1]	—	19·9 [2]
10-Methylundecanoic	41·4—41·5	108·1—108·4 [b]	23·38	24·13 [b]
	41·2 [1]	108 [1]	—	24·1 [2]
12-Methyltridecanoic	53·3—53·6	—	26·82	—
	53·4—53·6 [a]	108·1—108·3 [a]	26·80 [a]	27·14 [a]
	53·3 [1]	107·3 [1]	26·8,[2] 27·0 [3]	27·0,[2] 26·7 [3]
	53·3—53·6 [3]	—	—	—
16-Methylheptadecanoic	69·5—69·7	107·8—107·9	33·75	34·7
	69·5 [1]	107·3 [1]	33·8 [2,3]	35·0,[2] 34·5 [3]
18-Methylnonadecanoic	75·3—75·6	105·9—106·1	37·52	36·70
	75·3 [1]	105·1 [1]	37·8 [2]	36·8 [2]

* Specimens were prepared by the anodic method, unless indicated as [a] (Strong), [b] (Bowman), or [c] (Crombie and Harper).

[1] Weitkamp (*loc. cit.*). [2] Velick (*loc. cit.*). [3] Ställberg and Stenhagen (*loc. cit.*). [4] Nelson and Dawson (*J. Amer. Chem. Soc.*, 1923, **45**, 2179).

The long *X*-ray spacings were measured on a Philips high-angle Geiger counter spectrometer previously calibrated with a silicon standard. Filtered Cu-K_α radiation was used ($\lambda = 1{\cdot}541$ Å). The specimens were prepared by melting them between two microscope slides and allowing them to cool under slight pressure. For every specimen it was possible to observe at least ten orders of "reflection."

Experimental

M. p.s are corrected.

Anodic Syntheses.—These were carried out under the conditions described under "Method B1" (Linstead *et al.*, *loc. cit.*, p. 3328) with dry methanol as solvent.

Craig Counter-current Distribution Separation of a Mono- and Di-carboxylic Acid Mixture.—Pimelic acid (0·15 g.) and 10-methylundecanoic acid (0·15 g.) were introduced into tube No. 0 of a 25-tube steel counter-current apparatus containing a two-phase solvent system made up from hexane (100), acetone (25), ethanol (13), and water (62) (figures in parentheses denote parts by volume). After 24 transfers had been applied the contents of the tubes were evaporated, giving pimelic acid, m. p. 105—106°, in tubes 0—4 inclusive (peak in tube 1) and 10-methylundecanoic acid, m. p. 40—41°, in tubes 20—24 inclusive (peak in tube 23).

8-*Methylnonanoic acid* (II).—(a) *From* cis- *and* trans-2-iso*butyl*-3-*chlorotetrahydropyran*. A mixture of *cis*- and *trans-iso*butyl-3-chlorotetrahydropyrans (11·8 g., 0·067 mole), prepared by the reaction of *iso*butylmagnesium bromide with 2 : 3-dichlorotetrahydropyran, was treated with powdered sodium (5 g., 0·218 g.-atom) in dry ether following the procedure of Crombie and Harper (*loc. cit.*); the product was poured into water and extracted with ether, to yield after distillation 7-methyloct-4-en-1-ol (5·5 g., 58% based on the 2-alkyl-3-chlorotetrahydropyran), b. p. 107°/21 mm. (Found: C, 75·8; H, 12·8. Calc. for $C_9H_{18}O$: C, 76·0; H, 12·8%). Hydrogenation afforded 7-methyloctanol (Found: C, 74·6; H, 14·0. Calc. for $C_9H_{20}O$: C, 74·9; H, 14·0%), characterised as its phenylurethane, m. p. 65° (Cason, *J. Amer. Chem. Soc.*, 1942, **64**, 1102, records m. p. 65°). The 7-methyloctanol was converted into the bromide (3·5 g.; b. p. 107°/27 mm.) (Found: Br, 38·6. Calc. for $C_9H_{19}Br$: Br, 38·6%) with hydrogen bromide and thence through the nitrile into 8-methylnonanoic acid [cf. the preparation of (IV), method (*a*)] (1·03 g., 9% overall yield) (Found: C, 69·7; H, 11·7%; equiv., 173. Calc. for $C_{10}H_{20}O_2$: C, 69·5; H, 11·8%; equiv., 172·3). The amide had m. p. 103·8° (from acetone) (Found: C, 69·6; H, 12·7; N, 7·9. Calc. for $C_{10}H_{21}ON$: C, 70·1; H, 12·4; N, 8·2%).

(b) *From* 4-*methylpentanoic acid and ethyl hydrogen adipate*. The anodic method was used: 4-methylpentanoic acid (11·6 g., 0·1 mole), ethyl hydrogen adipate (33·6 g., 0·2 mole), and sodium (0·14 g., 0·006 g.-atom) were electrolysed to yield 8-methylnonanoic acid (6·58 g., 38% based on the 4-methylpentanoic acid), b. p. 106°/1 mm., f. p. 22·6° (from f. p. curve); after three recrystallisations from hexane at −50° it had m. p. 23·7—24·0°.

10-*Methylundecanoic Acid* (III).—(a) *From* 4-*methylpentanoyl chloride and benzyl pentane*-1 : 1 : 5 : 5-*tetracarboxylate*. Ethyl pentane-1 : 1 : 5 : 5-tetracarboxylate (36 g., 0·1 mole)

was heated under reflux in dry benzene (150 c.c.) with powdered sodium (2·3 g., 0·1 g.-atom) until all the latter had dissolved (6 hr.). Benzyl alcohol (43·2 g., 0·4 mole) was added and distillation effected through a Fenske-helices-packed column until the theoretical quantity of ethanol (0·4 mol.) had been removed as the benzene–ethanol azeotrope (5 hr.) (cf. Bowman, *loc. cit.*, and Nunn, *loc. cit.*). 4-Methylpentanoyl chloride (13·45 g., 0·1 mole) was added slowly with stirring while cooling with ice–water, and the mixture was then refluxed (1 hr.) and cooled. Distilled water (250 c.c.) was added and the organic layer was taken up in ether, separated, washed (water), and dried (Na_2SO_4). The solvents were removed in a vacuum at <40°, leaving a light yellow oil (70 g., 0·1 mole) which was shaken in dry ethanol–ethyl acetate (1 : 1; 200 c.c.) with hydrogen at 50 lb./sq. in. in the presence of palladium–calcium carbonate (10 g.; Pd, 1%); no hydrogen was absorbed; the catalyst was filtered off and replaced by the same amount of fresh catalyst which was filtered off after no hydrogen had been taken up; palladium–carbon (5 g.; Pd, 10%) was added and hydrogen was taken up (*ca.* 85% theor.) during 3 hours. The catalyst was filtered off and the solvents were removed in a vacuum; the residue was heated at 95° and then at 180° for a short period to complete the decarboxylation. The product was distilled through a short Vigreux column to give: (*a*) 6·65 g., b. p. 110°/25 mm., (*b*) 1·35 g., b. p. 110°/25 mm. to 85°/2 mm., (*c*) 1·8 g., b. p. 85—110°/2 mm., (*d*) 0·5 g., b. p. 127—135°/1 mm., (*e*) 5·3 g., b. p. 140—157°/1 mm., (*f*) 0·8 g., b. p. 157°/1 mm., (*g*) 1·3 g., b. p. 165—195°/1 mm. and (*h*) 1·3 g., b. p. 195—200°/1 mm. Fraction (*a*) contained *cyclo*hexanone (2 : 4-dinitrophenylhydrazone, m. p. 157°; semicarbazone, m. p. 165°; and oxime m. p. 89°; mixed m. p.s gave no depression) and 4-methylpentanoic acid (*p*-bromophenacyl ester, m. p. 79°; amide m. p. 117°; mixed m. p.s gave no depression). Fractions (*e*) and (*f*) contained the required 7-keto-10-methylundecanoic acid; they were combined and reduced without purification by Huang-Minlon's procedure (*loc. cit.*) to give a product from which 10-methylundecanoic acid (1·0 g., 5%), m. p. 40—41°, was separated by fractional distillation (b. p. 130°/1 mm.) followed by crystallisation from aqueous methanol (Found: C, 71·6; H, 12·1%; equiv., 201. Calc. for $C_{12}H_{24}O_2$: C, 72·0; H, 12·1%; equiv., 200·3); the amide was recrystallised from *iso*hexane to m. p. 108·1—108·4° (Found: C, 72·7; H, 12·7. Calc. for $C_{12}H_{25}ON$: C, 72·4; H, 12·55%). Fraction (*h*) contained pimelic acid which was purified by crystallisation from aqueous hydrochloric acid (m. p. and mixed m. p. 105°).

(b) *From 2-methylpropanoyl chloride and benzyl heptane-1 : 1 : 7 : 7-tetracarboxylate.* By the above procedure but starting with 0·15 mole of ester with the appropriate amounts of sodium, benzyl alcohol, and the acid chloride, 10-methylundecanoic acid was obtained in 2 g. (6·7%) yield together with some azelaic acid.

(c) *From 3-methylbutanoic acid and ethyl hydrogen azelate.* The anodic method was used: 3-Methylbutanoic acid (88 g., 0·86 mole), ethyl hydrogen azelate (88 g., 0·41 mole), and sodium (0·6 g., 0·03 g.-atom) were electrolysed. 10-Methylundecanoic acid (37 g., 45% based on the ethyl hydrogen azelate) was recovered by distillation (b. p. 130°/1 mm.). After recrystallisation from 96% ethanol it had m. p. 41·4—41·5° and gave no depression of m. p. in admixture with the specimen supplied by Dr. Weitkamp.

12-*Methyltridecanoic Acid* (IV).—(a) *From 6-methylhept-1-yne and 1-chloro-5-iodopentane.* 6-Methylhept-1-yne (44 g., 0·4 mole) was added to sodamide (from 10 g., 0·435 g.-atom of sodium) in liquid ammonia and 1-chloro-5-iodopentane (93 g., 0·32 mole) was subsequently added (cf. Strong *et al.*, *loc. cit.*). After 24 hours the product was worked up, to yield 1-chloro-11-methyldodec-6-yne, b. p. 80°/1 mm. (24 g., 35% based on the 1-chloro-5-iodopentane), which was refluxed with ethanol (95%; 300 c.c.) for 72 hours with sodium cyanide (15 g., 0·31 mole); the precipitated sodium chloride was filtered off and the filtrate refluxed for 120 hours with sodium hydroxide (9·5 g., 0·24 mole) in water (50 c.c.). The 12-*methyltridec-7-ynoic acid* so produced was freed from non-acids by extraction of its alkaline solution (in 20% aqueous ethanol) with ether in the usual way and distilled, having b. p. 150—151°/1 mm. (11·8 g., 48% based on the 11-methyl-1-chlorododec-6-yne) [Found: C, 74·6; H, 10·6%; equiv., 219; 0·2598 g. took up 52·7 c.c. of H_2 (N.T.P.). $C_{14}H_{24}O_2$ requires C, 74·95; H, 10·8%; equiv., 224·3; 0·2598 g. is equivalent to 52·0 c.c. of H_2]; the acid had n_D^{30} 1·4556, d_4^{30} 0·91604, $[R_L]_D$ 66·5. (Calc. 66·4). Its p-*bromophenacyl* ester had m. p. 51° (from aqueous ethanol) (Found: C, 62·5; H, 6·95; Br, 19·0. $C_{22}H_{29}BrO_3$ requires C, 62·7; H, 6·9; Br, 19·0%). The acetylenic acid was smoothly hydrogenated in ethyl acetate in the presence of Adams's catalyst, to yield 12-methyltridecanoic acid, recrystallised from acetone and then hexane to m. p. 53·4—53·6°, b. p. 158°/2 mm. (Found: C, 73·6; H, 12·5%; equiv., 226. Calc. for $C_{14}H_{28}O_2$: C, 73·6; H, 12·4%; equiv., 228·4), characterised as its amide, m. p. 108·1—108·3° (from hexane) (Found: C, 74·0; H, 12·6. $C_{14}H_{29}ON$ requires C, 73·9; H, 12·85%).

(b) *From 4-methylpentanoic acid and ethyl hydrogen sebacate.* The anodic method was used: 4-methylpentanoic acid (23 g., 0·2 mole), ethyl hydrogen sebacate (46 g., 0·2 mole), and sodium (0·2 g., 0·009 g.-atom) were electrolysed, to yield 12-methyltridecanoic acid, recrystallised as above to give m. p. 53·3—53·6° (12 g., 27%) (Found: equiv., 225·5. Calc. for $C_{14}H_{28}O_2$: equiv., 228·4).

16-*Methylheptadecanoic Acid* (V).—12-Methyltridecanoic acid (5 g., 0·022 mole), ethyl hydrogen adipate (16·8 g., 0·1 mole), and sodium (0·1 g., 0·004 g.-atom) were electrolysed, to yield 16-methylheptadecanoic acid (3 g., 47% based on the 12-methyltridecanoic acid) contaminated with sebacic acid. The latter was removed by counter-current distribution in a Craig apparatus with the two-phase solvent system detailed above; after 11 transfers the last two tubes contained the bulk of the 16-methylheptadecanoic acid, showing its preferential partition in the hydrocarbon layer; the acid had m. p. 68·0—68·7° and was recrystallised from acetone and then from hexane to m. p. 69·5—69·7° (Found: C, 75·8; H, 12·7%; equiv., 286. Calc. for $C_{18}H_{36}O_2$: C, 76·0; H, 12·6%; equiv., 284·5). The amide had m. p. 107·8—107·9° (from acetone and hexane) (Found: N, 4·7. Calc. for $C_{18}H_{37}ON$: N, 4·9%).

18-*Methylnonadecanoic Acid* (VI).—10-Methylundecanoic acid (34 g., 0·17 mole), ethyl hydrogen sebacate (113 g., 0·49 mole), and sodium (0·3 g., 0·01 g.-atom) were electrolysed, to yield 18-methylnonadecanoic acid (19 g., 36% based on the 10-methylundecanoic acid) (Found: C, 76·6; H, 12·9%; equiv., 312. Calc. for $C_{20}H_{40}O_2$: C, 76·7; H, 12·9%; equiv., 312·5), recrystallised from 96% ethanol to m. p. 75·3—75·6°, alone or mixed with the specimen supplied by Dr. Weitkamp. The amide had m. p. 105·9—106·1° (from acetone) (Found: N, 4·5. Calc. for $C_{20}H_{41}ON$: N, 4·5%).

The authors thank Dr. W. S. Rapson for suggesting this work, Dr. A. W. Weitkamp for the gift of 10-methylundecanoic and 18-methylnonadecanoic acid, and Mr. F. W. G. Schöning for carrying out the microanalyses. *X*-Ray measurements were made by Dr. J. N. van Niekerk and Mr. F. R. L. Schöning. This paper is published by permission of the South African Council for Scientific and Industrial Research.

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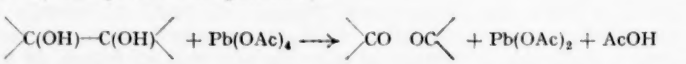
17. *The Oxidation of Glycols with Lead Tetra-acetate. A Kinetic Study.*

By J. P. Cordner and K. H. Pausacker.

The rates of oxidation of a number of glycols by lead tetra-acetate have been measured in glacial acetic acid solution. The oxidation of ethylene glycol in aqueous acetic acid of varied composition has also been studied. A modification of the currently accepted mechanism of this reaction is proposed.

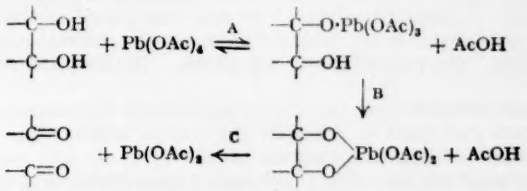
Although lead tetra-acetate is a very versatile oxidising agent (Criegee, "Newer Methods of Preparative Organic Chemistry," Interscience Publ., 1948, p. 1), perhaps its principal use is in the oxidation of glycols. Aldehydes or ketones are thus formed under very mild conditions (usually room temperature):



Bell, Sturrock, and Whitehead (*J.*, 1940, 82) have found that this reaction is of first-order with respect to both glycol and lead tetra-acetate in acetic acid solution. Criegee (*Sitzungsber. Ges. Naturwiss. Marburg*, 1934, **69**, 26) has also found that the overall reaction is of second order in acetic acid but of a complex order when any other solvent is used. In addition, the rate of reaction is increased, by a factor of about 10^3, when acetic acid is replaced by benzene, nitrobenzene, 1 : 2-dichloroethane, or 1 : 1 : 2 : 2-tetrachloroethane.

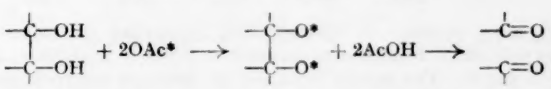
Two other important points noted by Criegee are (*a*) that *cis*-glycols react more readily than the corresponding *trans*-compounds, the difference being more marked in 5-membered than in 6-membered rings, and (*b*) that lead tetra-acetate reacts with methyl alcohol, containing a small quantity of water, forming $Pb(OAc)_2(OH)(OMe)$.

On the basis of these results, Criegee, Kraft, and Rank (*Annalen*, **1933**, **507**, 159) proposed the following mechanism :



By assuming that stage (B) is rate-determining, they were able to satisfy both the second-order kinetics and the fact that a *cis*-glycol reacts more readily than its *trans*-isomer. Furthermore, the isolation of $Pb(OAc)_2(OH)(OMe)$ (see above) appears to support stage (A).

This mechanism was criticised by Waters (" Chemistry of Free Radicals," Oxford, 1946, p. 230) who proposed the following :



Although Waters satisfactorily explained the second-order kinetics, Kharasch, Friedlander, and Urry (*J. Org. Chem.*, **1949**, **14**, 91) disproved this alternative suggestion by showing that acetyl peroxide (which definitely furnishes acetoxy-radicals) does not cause glycol fission.

Although Criegee and his co-workers have oxidised a large number of glycols, there has been no attempt to investigate the effect of substituents in simple aromatic glycols. The present work is concerned, *inter alia*, with the oxidation of tetra-substituted benzopinacols, which were chosen as they do not display optical isomerism.

Experimental

Reagents.—Lead tetra-acetate, prepared by Bailar's method (" Inorganic Syntheses," McGraw-Hill, 1939, Vol. 1, p. 47), was crystallised from acetic acid and stored in a desiccator under vacuum. The minimum purity (estimated by iodometric titration, see below) was 97·5%.

Acetic acid was purified by Eichelberger and LaMer's method (*J. Amer. Chem. Soc.*, **1933**, **55**, 3633). The m. p. was always in the range 16·0—16·2°, corresponding to 0·2—0·3% of water (Rudorff, *Ber.*, **1870**, **3**, 390). Water was twice distilled from potassium permanganate in an all-glass apparatus. All glycols were either distilled, or crystallised, twice : ethylene glycol, b. p. 177°, n_D^{19} 1·4289; propylene glycol, b. p. 186°, n_D^{20} 1·4310; glycerol α-monochlorohydrin, b. p. 129°, n_D^{21} 1·4778; (±)-*iso*butyl tartrate, m. p. 70°; pinacol hydrate, m. p. 46°; pinacol, m. p. 40°; benzpinacol, m. p. 185°; 4 : 4′ : 4″ : 4‴-tetramethoxybenzpinacol, m. p. 181°; 4 : 4′ : 4″ : 4‴-tetrachlorobenzpinacol, m. p. 173°; 4 : 4′ : 4″ : 4‴-tetramethylbenzpinacol, m. p. 183°.

Apparatus.—A bath was used whose temperature was controlled within ±0·05°. The slow reactions were performed in a calibrated standard 50-ml. flask (slow method) and the fast reactions in a " Dreischenkelrohr " (Criegee, *Annalen*, 1932, **495**, 219) (fast method).

Methods of Estimation.—Slow method. The glycol (*ca.* 10^{-3} mole) was weighed into the reaction vessel, which was brought to the temperature of the bath. A solution of lead tetra-acetate (*ca.* 2·5—3·0 × 10^{-2}M) in acetic acid, also heated in the bath, was added to make up to the mark. When the glycol dissolved slowly, it was first dissolved in acetic acid in the flask and then a known volume of a solution of lead tetra-acetate was added, along with acetic acid to make up to the mark, so that the resulting molarities were the same as quoted above. 5-Ml.

aliquots were withdrawn at determined times and added to 4—5 ml. of "stopping solution," *i.e.*, potassium iodide (100 g.) and sodium acetate (500 g.) dissolved in water (1 l.). The iodine liberated was titrated with 0·02N-sodium thiosulphate (starch). It was unnecessary to filter off the precipitated lead iodide as recommended by Bell, Sturrock, and Whitehead (*loc. cit.*). The lead tetra-acetate solution was also estimated.

Fast method. Previously determined solutions (3 ml. of each) of lead tetra-acetate (*ca.* 2·5—3·0 $\times$ 10^{-2}M) and glycol (*ca.* 2 $\times$ 10^{-2}M) in acetic acid were placed in each of the lower bulbs of the "Dreischenkelrohr." "Stopping solution" (4 ml.) was placed in the side bulb. After attaining temperature equilibrium in the bath (10 minutes), the reacting solutions were mixed and, at a definite time, the "stopping solution" was added. The liberated iodine was estimated as above.

The lead tetra-acetate solutions were found to be stable under the various conditions used.

All experiments were performed in duplicate (agreement within 5%), and the accuracy obtained by the two methods is approximately the same.

Results.—The reaction of ethylene glycol with lead tetra-acetate, in acetic acid containing 10 moles % of water, at 25° is given below as a typical example; the slow method was used.

Initial glycol concn. = 0·01966M ($\equiv$ 7·845 ml. $Na_2S_2O_3$).
Initial lead tetra-acetate concn. = 0·02629M ($\equiv$ 10·495 ml. $Na_2S_2O_3$).
First lead tetra-acetate estimation = 9·730 ml. (*b*).
Equivalent glycol concn. = 7·080 ml. (*a*).

Time (min.)	70	110	150	210	270	330	420
Titre obs.	8·55	8·04	7·60	7·03	6·58	6·20	5·72
Titre calc.	8·56	8·06	7·61	7·04	6·58	6·18	5·71

By plotting $\log_{10} a(b - x)/b(a - x)$ against t and calculating the slope by the method of least squares, k was calculated from the equation $k = 2{\cdot}303 \times \text{slope}/(b - a)$ and found to be $1{\cdot}84 \times 10^{-3}$ mole^{-1} l. sec.$^{-1}$. The results obtained at different temperatures are summarised below (averages in parentheses):

Temp.	35·15°	25·00°	17·90°
10^3k	6·55, 6·13 (6·34)	1·93, 1·83 (1·88)	0·695, 0·714 (0·704)

The bimolecular constants obey the Arrhenius equation as shown by the following data, where the calculated values are given by $k = 7{\cdot}75 \times 10^{13}\, e^{-22{,}610/RT}$:

Temp.	35·15°	25·00°	17·90°
10^3k obs.	6·34	1·88	0·705
10^3k calc.	6·37	1·80	0·708

The results obtained with different glycols in acetic acid (0·2—0·4% of water) are summarised in Table 1, duplicates being shown:

TABLE 1.

Compound	Temp.	$k \times 10^3$	$10^{-14}A$	E (kcal.)	Compound	Temp.	$k \times 10^3$	$10^{-10}A$	E (kcal.)
Ethylene glycol *	18°	0·408, 0·379	17·1	22·1	Benzpinacol †	18°	95·4, 89·5	16·6	13·6
	25	1·02, 1·04				25	160, 161		
	35	3·23, 3·35				35	328, 354		
Propylene glycol *	18	4·06, 3·66	1·82	22·1	4 : 4′ : 4″ : 4‴-Tetramethoxybenzpinacol †	18	383, 367	43·2	13·4
	25	9·39, 9·67				25	618, 581		
	35	33·8, 31·0				35	1290, 1390		
Glycerol α-monochlorohydrin *	18	1·70, 1·61	6·55	23·4	4 : 4′ : 4″ : 4‴-Tetramethylbenzpinacol †	18	160, 174	9·09	15·3
	25	4·32, 4·54				25	329, 337		
	35	16·1, 14·7				35	715, 773		
*iso*Butyl tartrate *	18	2·12, 2·38	38·2	20·2	4 : 4′ : 4″ : 4‴-Tetrachlorobenzpinacol †	18	49·1, 47·1	3·30	15·7
	25	5·29, 4·85				25	93·4, 88·8		
	35	15·7, 15·5				35	216, 226		
Pinacol *	18	6·44, 5·78	7·34	22·7					
	25	14·8, 14·7							
	35	53·0, 53·0							
Pinacol hydrate *	18	5·34, 5·18	1·59	23·2					
	25	13·9, 14·6							
	35	48·6, 48·4							

* By slow method. † By fast method.

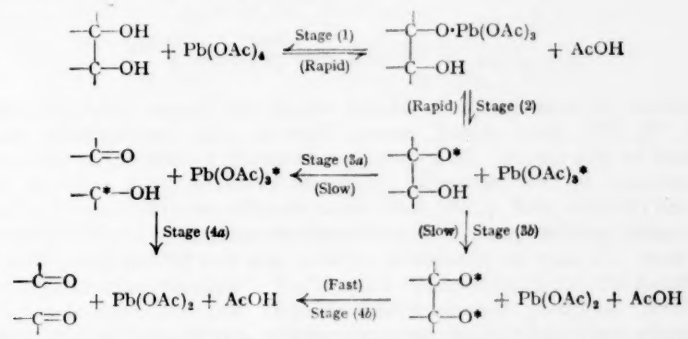
The results obtained with ethylene glycol in aqueous acetic acid are summarised below, duplicate values of k being shown:

TABLE 2.

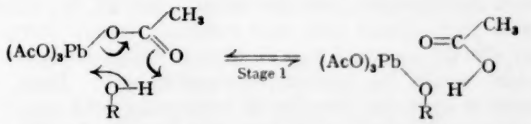
H_2O, moles %	T	$k \times 10^3$	A	E (kcal.)	H_2O, moles %	T	$k \times 10^3$	A	E (kcal.)
1	18°	0·408, 0·379	$1·73 \times 10^{13}$	22·1	20	18°	1·08, 1·08	$4·71 \times 10^{13}$	23·4
	25	1·02, 1·04				25	3·04, 2·70		
	35	3·23, 3·35				35	10·60, 10·66		
5	18	0·550, 0·522	$1·42 \times 10^{13}$	21·5	30	18	1·73, 1·96	$3·24 \times 10^{14}$	23·0
	25	1·26, 1·37				25	4·13, 4·50		
	35	4·47, 4·39				35	15·6, 14·9		
10	18	0·695, 0·714	$7·75 \times 10^{13}$	22·6	40	18	3·76, 3·75	$9·20 \times 10^{10}$	17·8
	25	1·93, 1·83				25	7·91, 8·34		
	35	6·70, 6·25, 6·08				35	21·4, 20·0		

DISCUSSION

Although Criegee has shown that his mechanism is concordant with the observed second-order kinetics, it is naturally possible to formulate many mechanisms which satisfy this requirement. The following mechanisms are satisfactory in this regard and it is desired to compare them with Criegee's formulation.



It is thus seen that stage (1) is the esterification proposed by Criegee and the following scheme is proposed :



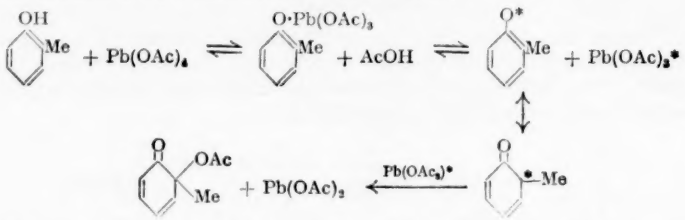
The present work supports Criegee's arguments for the validity of this stage because it is seen that, with the substituted benzpinacols, electron-releasing groups (Me, OMe), accelerate the reaction whereas an electron-attracting group (Cl) retards it. This is in accord with the fact that the Pb–OR bond formation would be favoured by increased availability of electrons on the oxygen atom, thus displacing the equilibrium to the right. Furthermore, work on aryl iodosoacetates strongly supports this view (see following paper) as it has been found that the rate is increased when an electron-attracting group is on the aryl nucleus and decreased when an electron-donating group is present.

Stage (2) represents a normal dissociation of quadrivalent lead compounds which has already been postulated by many authors (cf. Kharasch, Friedlander, and Urry, *J. Org. Chem.*, 1951, **16**, 533).

Stage (3*a*) is analogous to the decomposition of the *tert.*-butyloxy-radical into methyl radical and acetone (Raley, Rust, and Vaughan, *J. Amer. Chem. Soc.*, 1948, **70**, 88). However, it is incorrect to assume this stage, for it was found that lead tetra-acetate remained unchanged in the presence of *tert.*-butyl alcohol and triphenylmethanol. As Merz and Waters (*J.*, 1949, S 21) have found that Fenton's reagent readily oxidises *tert.*-butyl alcohol, stage (3*a*) must be abandoned, as it is similar to the established intermediates involved in oxidation by Fenton's reagent. Consequently, stage (3*b*) is preferred and this may be

regarded as being simultaneous with stage (2). It is thus seen that the products resulting from stage (3*b*), and their subsequent decomposition, are the same as those that have already been postulated by Waters (*op. cit.*) for this reaction.

A homolytic fission is to be preferred in place of Criegee's cyclisation mechanism for the following reasons. (*a*) Lead tetra-acetate displays radical reactions in glycol fission which are consistent with nearly all other reactions of this compound. (*b*) The oxidation of phenols by lead tetra-acetate in acetic acid (Wessely, Lautebach-Kiel, and Sinwel, *Monatsh.*, 1950, **81**, 811; Wessely and Sinwel, *ibid.*, p. 1055) can be explained by the same type of mechanism. These authors found that phenols are oxidised to derivatives of *cyclo*hexadienone at room temperature; *e.g.*, *o*-cresol yields 2-acetoxy-2-methyl*cyclo*hexa-3 : 5-dien-1-one. This reaction is now assumed to occur as follows:



(*c*) The oxidation of *trans*-decalin-9 : 10-diol, which, as Criegee, Büchner, and Walther (*Ber.*, 1940, **73**, 571) have stated, cannot form a cyclic intermediate, can now be accommodated by this theory. It is no longer necessary to assume, as these authors do, that the oxidation of this particular compound proceeds by a different mechanism. (*d*) Criegee and Büchner (*ibid.*, p. 563) have found that the pinacols formed by the reduction of *cyclo*pentanone, *cyclo*hexanone, and *cyclo*heptanone are oxidised more rapidly the larger the ring system. It may be possible to explain this fact by assuming that the initial homolytic fission will occur more readily if the attached rings are large enough to strain the bonds involved. Similarly, the observed increase in rate (and decrease in A and E) of aromatic glycols, compared with aliphatic compounds, may be explained (see Table 1).

However, the crucial point that has not yet been explained on the basis of this mechanism is the fact that *cis*-glycols react more readily than *trans*-compounds. It has been shown (Martinet and Martinet, *Bull. Soc. chim.*, 1949, **57**, 71; Bastiansen, *Acta Chem. Scand.*, 1949, **3**, 415) that glycols with free rotation display intramolecular hydrogen bonding. It would also be expected that *cis*-glycols would display this type of bonding whereas *trans*-glycols would be bonded intermolecularly. Thus, whereas only one hydrogen participates in hydrogen bonding in *cis*-glycols, both may participate in *trans*-glycols with a consequent diminution in rate (for further discussion of this point, see following paper).

It is seen (Table 2) that the variations of A and E with solvent composition were markedly similar. It is possible that the initial increase in A and E is due to a change in the dielectric constant of the medium but, after a critical value of *ca.* 25 moles% of water, the water molecules tend to replace acetic acid in the solvating atmosphere, with a subsequent decrease in A and E. This is in contrast to the explanation given by Criegee and Büchner (*loc. cit.*) that "nascent" lead dioxide is the oxidising agent.

Finally, we think some of Criegee's results should be regarded with caution. For example (*Sitzungsber. Ges. Naturwiss. Marburg*, 1934, **69**, 26), he has investigated no fewer than 18 reactions whose half-time is less than 10 seconds solely by means of a "Dreischenkelrohr." The rate constants given for these reactions are meaningless. In addition, nearly all his A and E values have been determined from measurements made at only two temperatures, and the water content of his acetic acid has never been rigidly specified except in the one paper by Criegee and Büchner (*loc. cit.*)

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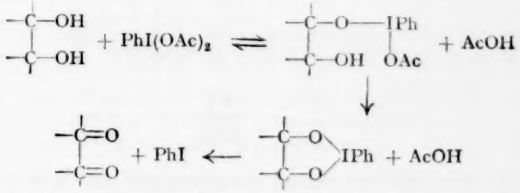
18. *The Oxidation of Glycols by Aryl Iodosoacetates. A Kinetic Study.*

By K. H. Pausacker.

The rates of oxidation of *iso*hydrobenzoin by aryl iodosoacetates in acetic acid have been measured. The results obtained were in accord with the general conclusions made on glycol oxidation in the previous paper.

Criegee and Beucker (*Annalen*, 1939, **541**, 218) investigated the reactions of compounds of the type $RI(O{\cdot}COR')_2$ (where R = aryl; R′ = alkyl or aryl) and found that they resemble lead tetra-acetate in their general reactions. These authors paid particular attention to the formation of glycol diacetates from olefins, and the oxidation of glycols forming carbonyl compounds. Their mechanism for the oxidation of glycols is similar to that proposed by Criegee for lead tetra-acetate oxidation (see preceding paper) as shown below:



The present work is concerned with the oxidation of *iso*hydrobenzoin by aryl iodosoacetates in acetic acid solution.

Experimental

Preparation of Aryl Iodosoacetates.—Willgerodt's general method (*J. pr. Chem.*, 1886, **33**, 156; 1899, **59**, 198) was used, the aryl iodide being converted into the iododichloride which is hydrolysed to the iodoso-compound, treatment of which with acetic acid yields the iodosoacetate. The following substituted phenyl iodosoacetates were prepared.

Substituent	M. p. Found	M. p. Lit.	Equiv.: Found	Equiv.: Calc.	Substituent	M. p. Found	M. p. Lit.	Equiv.: Found	Equiv.: Calc.
—	158°	158°	161	161	*p*-Cl *	104°	—	179	178
p-Me *	104	—	166	168	*m*-Cl	154	155°	176	178
m-Me	154	148	166	168	*m*-NO_2	155	155	183	183·5

* New compounds.

Phenyl iodosoacetate is best prepared by a modification of the method suggested by Böeseken and Schneider (*ibid.*, 1931, **131**, 285). Hydrogen peroxide (30%, 70 ml.) and acetic anhydride (305 ml.) were stirred together for 4 hours at 40°. Iodobenzene (50 g.) was added to the solution, which was then kept overnight. Some phenyl iodosoacetate crystallised and was filtered off; the filtrate was concentrated to a small volume under reduced pressure (70 mm.), and a second crop obtained. The combined crystals were washed with ether and dried (NaOH) in a vacuum desiccator (yield 52 g.; m. p. 158°).

Acetic acid was purified as described in the preceding paper.

*iso*Hydrobenzoin was prepared by catalytic reduction of benzoin (Buck and Jenkins, *J. Amer. Chem. Soc.*, 1929, **51**, 2163), m. p. 134°.

Apparatus and Method of Estimation.—A bath was used whose temperature was controlled within ±0·05°. *iso*Hydrobenzoin (0·16—0·20 g.) was accurately weighed into a 50-ml. standard flask. When the flask had attained the temperature of the bath, a 0·02M-acetic acid solution of the aryl iodosoacetate, previously heated to the temperature of the bath, was added to make up to the mark. When the *iso*hydrobenzoin had dissolved, 5-ml. aliquots were withdrawn at determined times and added to acidified potassium iodide solution. The liberated iodine was titrated with 0·02N-sodium thiosulphate solution (starch). The initial aryl iodoso-

acetate solution was estimated in the same way. All experiments were run in duplicate, and agreement was generally within 5%.

Results.—The reaction of phenyl iodosoacetate with *iso*hydrobenzoin af 45·4° has been chosen as a typical example.

Wt. of *iso*hydrobenzoin = 0·1757 g. (≡ 8·12 ml. 0·02018N-$Na_2S_2O_3$).
Initial phenyl iodosoacetate titre = 9·84 ml.
First phenyl iodosoacetate estimation = 8·40 ml. (*a*).
Equivalent *iso*hydrobenzoin concn. = 6·68 ml. (*b*).

Time (min.)		25	50	75	100	125	150	200
Titre	obs.	7·35	6·56	5·97	5·45	5·02	4·67	4·17
	calc.	7·38	6·55	5·91	5·39	5·06	4·72	4·14

By the method given in the preceding paper (p. 104), it was found that $k = 7{\cdot}28 \times 10^{-3}$ mole^{-1} l. sec.$^{-1}$.

The results obtained at different temperatures are summarised herewith, means being given in parentheses:

Temp.	24·8°	34·7°	45·4°
10^3k	0·692, 0·660 (0·676)	2·14, 2·09 (2·12)	7·28, 6·70 (6·99)

The bimolecular constants obey the Arrhenius equation as shown by the following data, where the calculated values are given by $k = 3{\cdot}39 \times 10^{12}e^{-21,330/RT}$:

Temp.		24·8°	34·7°	45·4°
10^3k	obs.	0·676	2·12	6·99
	calc.	0·692	2·14	7·08

The results obtained with different phenyl iodosoacetates and *iso*hydrobenzoin in acetic acid are summarised below:

Substituent	T	$k \times 10^3$	$10^{-13}A$	E (kcal.)	Substituent	T	$k \times 10^3$	$10^{-13}A$	E (kcal.)
p-Me	34·7°	1·57, 1·61	36·3	21·6	*p*-Cl	24·9°	1·84, 1·69	1·48	21·6
	45·4	5·16, 5·28				30·5	3·57, 3·55		
	52·8	11·3, 11·4				34·7	5·56, 5·52		
m-Me	34·7	1·77, 1·86	26·3	21·3	*m*-Cl	24·5	2·63, 2·63	4·17	22·0
	45·6	5·40, 5·71				29·9	5·20, 5·03		
	52·9	12·5, 13·0				34·7	9·11, 8·99		
—	24·8	0·692, 0·660	33·9	21·3	*m*-NO_2	25·1	8·61, 8·46	93·3	20·5
	34·7	2·14, 2·09				30·0	13·3, 13·0		
	45·4	7·15, 6·64				34·7	24·5, 25·5		

Discussion

It is seen that the six compounds investigated have A and E values which are very close to each other as may, perhaps, be expected with the interaction of such large molecules. However, when the k values at 34·7° are compared, it is found that electron-repelling groups decrease the rate of reaction and electron-attracting groups have the opposite effect. Furthermore, it is found that a good linear plot is obtained when Hammett's equation is applied.

This is in accord with the type of mechanism proposed for lead tetra-acetate in the preceding paper, *viz.*,

It is thus seen that if electron-attracting groups are present in the aryl group, then the equilibrium in stage 1 will lie further to the right with a consequent increase in rate.

We have also found (unpublished results) that phenyl iodosoacetate converts many primary aromatic amines into the corresponding azobenzenes, in agreement with Neu (*Ber.*, 1939, **72**, 1507) who found that azobenzene can be prepared from aniline and phenyl

iodosoacetate. By analogy with the oxidation of glycols this reaction may proceed as follows:

$$2PhI(OAc)_2 + 2Ar{\cdot}NH_2 \rightleftharpoons 2PhI(OAc)(NHAr) + 2AcOH$$

$$\Downarrow$$

$$2PhI(OAc)^{\bullet} + Ar{\cdot}NH{\cdot}NH{\cdot}Ar \longleftarrow 2Ar{\cdot}NH^{\bullet} + 2PhI(OAc)^{\bullet}$$

$$\downarrow$$

$$2PhI + 2AcOH + Ar{\cdot}N{:}N{\cdot}Ar$$

A preliminary investigation of the reaction of phenyl iodosoacetate with phenols in benzene solution has also yielded interesting results. At room temperature, *m*- and *p*-nitrophenol were rapidly oxidised, whereas *o*-nitrophenol remained unchanged. This further demonstrates the importance of hydrogen-bonding on the rate of reaction which has been discussed in the previous paper in relation to the relative rates of reaction of *cis*- and *trans*-glycols. The argument is more valid in the present instance as the reaction has been performed in benzene—a non-polar solvent. Thus the phenolic group in *o*-nitrophenol would be mainly hydrogen-bonded, whereas in the *m*- and *p*-compounds it would exist, at least partly, in the free state.

It was also found that phenyl iodosoacetate readily reacts with *iso*propyl alcohol, ethyl alcohol, and methyl alcohol in order of decreasing reactivity but is quite stable in *tert.*-butyl-alcoholic solution. This is in accord with the results obtained with the action of lead tetra-acetate on these compounds (see preceding paper).

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19. *Molecular Polarisation and Molecular Interaction. Part V. The Apparent Dipole Moments of Mesidine, Aminodurene, and Methylmesidine in Benzene and Dioxan Solutions.*

By J. W. SMITH.

Measurements of the dielectric constants, specific volumes, and refractive indices of dilute solutions at 25° show that the apparent dipole moments of mesidine, aminodurene, and methylmesidine are 1·45, 1·45, and 1·22 D, respectively, in benzene solution and 1·57, 1·57, and 1·26 D, respectively, in dioxan solution. The lower values relative to those for aniline and methylaniline are interpreted as indicating that mesomerism is inhibited appreciably with mesidine and aminodurene and to a considerable extent with methylmesidine. Comparison of the two series confirms that a large increase in molecular polarisation accompanies hydrogen bonding only when mesomeric effects are possible in at least one of the molecular species involved. Possible reasons for the inhibition of resonance in mesidine and aminodurene but not in 2 : 4 : 6-tribromoaniline or in mesitaldehyde are discussed.

IN Parts I, II, and IV (*J.*, 1949, 753, 2663; 1950, 3532) it was shown that the apparent molecular polarisations of aniline, *p*-chloro- and 2 : 4 : 6-tribromo-aniline, methylaniline, and diphenylamine are all much higher in dioxan than in benzene solution, whilst for *NN*-dimethyl- and 2 : 4 : 6-tribromo-*NN*-dimethyl-aniline and *n*- and *tert.*-butylamine there is little difference between the values in the two solvents. These higher molecular polarisations and the consequent higher apparent dipole moments in dioxan solution were attributed to hydrogen bonding between the amino-hydrogen atoms of the primary and secondary arylamines and the oxygen atoms of the dioxan molecules. Large increases in the apparent dipole moment have also been observed with diphenylamine in the presence of triethylamine or of pyridine (Part IV) and with alcohols in the presence of pyridine (*Chem. and Ind.*, 1948, 29). These results suggested that an appreciable increase in molecular polarisation results from hydrogen bonding only when at least one of the species

involved has a highly polarisable electronic system. For the arylamines this polarisation is most likely to occur through an increase in the mesomeric effect of the amino-group, which in turn implies that the molecules must be able to adopt a structure in which the amino-hydrogen atoms approach coplanarity with the aromatic ring.

This raises a particular interest in amines for which steric inhibition of resonance may occur. Birtles and Hampson (*J.*, 1937, 10) and Ingham and Hampson (*J.*, 1939, 981) found the dipole moments of aminodurene and mesidine in benzene to be 1·39 and 1·40 D, respectively, values appreciably less than that for aniline. On the other hand, the moment of bromodurene differed but little from that of bromobenzene, a circumstance which led Ingham and Hampson to infer that it was the steric effect of the *o*-methyl groups in hindering the formation of resonance structures involving N=C double bonds which caused the moments of aminodurene and mesidine to be less than that of aniline.

It was observed in Part II, however, that the dipole moment of 2 : 4 : 6-tribromoaniline in benzene is considerably greater than that of aniline, whilst the apparent value in dioxan solution is much greater than that in benzene, suggesting that the hydrogen-bonding of the amino-hydrogen atoms results in an increased mesomeric effect. It was therefore of interest to study the apparent dipole moments of mesidine and aminodurene in dioxan as well as in benzene, and also to determine the apparent moments in the two solvents of methylmesidine, which would be expected to form hydrogen bonds to the dioxan molecules but with which there should be very considerable inhibition of the mesomeric effect. No previous measurements on this compound have been reported.

Experimental

Materials.—Benzene and dioxan were purified as described in Part I (*loc. cit.*).

Mesidine. Nitromesitylene, prepared from mesitylene by Powell and Johnson's method (*Org. Synth.*, 1943, Coll. Vol. II, p. 449), was reduced with iron in the presence of a little water and a trace of acetic acid. The product, after addition of ammonia, was extracted with alcohol, the extract being acidified with hydrochloric acid and evaporated. The mesidine hydrochloride was twice recrystallised, and the base, liberated by sodium hydroxide, was distilled under reduced pressure and dried (CaO); it had b. p. 227°/762 mm. (lit., 227—230°).

Aminodurene. Durene was brominated by Smith and Moyle's method (*J. Amer. Chem. Soc.*, 1933, **55**, 1676), and the resulting bromodurene nitrated as described by Smith and Tenenbaum (*ibid.*, 1935, **57**, 1293). The bromonitrodurene was reduced to aminodurene with tin and hydrochloric acid in glacial acetic acid solution (Birtles and Hampson, *loc. cit.*), and after addition of sodium hydroxide the base was steam-distilled and recrystallised from alcohol; it had m. p. 72·0° (lit., 71—75°).

Methylmesidine. Mesidine was methylated with methyl sulphate (Ullmann, *Annalen*, 1903, **327**, 104), the product being purified through the nitrosamine, which was reduced with stannous chloride. After addition of sodium hydroxide the amine was steam-distilled and dried (CaO); it had b. p. 229°/755 mm. (Ullmann gives 228—229°/730 mm.).

Experimental Methods.—The dielectric constants and specific volumes were determined as in the previous investigations, and refractive indices for the Na-*D* line were measured with a Hilger Abbé refractometer.

Results.—The measurements are recorded in Table 1, where the symbols have their usual significance. The parameters α, β, and ν (the limiting values of $d\varepsilon/dw$, dv/dw, and dn^2/dw, respectively, at zero concentration) and the values of $P_{2\infty}$ and $[R_D]$ derived from them are given in Table 2. The values so deduced are in each case in accord with those calculated from the measurements at each concentration. The dipole-moment values given under μ are calculated on the assumption that $P_{E+A} = [R_D]$, and those under μ' are based on the arbitrary assumption that $P_{E+A} = 1{\cdot}05[R_D]$.

Discussion

Previous values for the dipole moments in benzene of mesidine (1·40 D; Ingham and Hampson) and aminodurene (1·39 D; Birtles and Hampson) are slightly lower than those now reported. This is explained partially by the use of the older values of the universal constants in their calculations. It is confirmed, however, that these moments are appreciably less than the dipole moment of aniline, lying between the latter and the value for primary alkylamines. This comparison is illustrated by the data collected in Table 3,

TABLE 1.

$100w$	ε	v	n_D	β (c.c.)	P_2 (c.c.)	r (c.c.)	R_2 (c.c.)
			Mesidine in benzene.				
0·0000	2·2725	1·14458	1·4979	0·34090	—	0·33544	—
1·6399	2·3023	1·14296	1·4987	0·34597	87·9	0·33542	45·2
3·2272	2·3316	1·14142	1·4994	0·35089	88·0	0·33537	45·0
4·5604	2·3573	1·14012	1·5000	0·35515	88·3	0·33533	45·0
6·0510	2·3850	1·13865	1·5007	0·35964	88·0	0·33529	45·0
7·4051	2·4111	1·13733	1·5013	0·36383	88·0	0·33525	45·0
			Mesidine in dioxan.				
0·0000	2·2041	0·97280	1·4199	0·27862	—	0·24612	—
0·8987	2·2267	0·97338	1·4212	0·28250	96·1	0·24694	45·5
1·8117	2·2499	0·97400	1·4225	0·28645	96·1	0·24777	45·5
3·0125	2·2808	0·97476	1·4241	0·29164	96·1	0·24879	45·2
4·9594	2·3313	0·97594	1·4270	0·29997	95·9	0·25057	45·4
6·0854	2·3810	0·97715	1·4299	0·30802	96·1	0·25237	45·7
			Aminodurene in benzene.				
0·0000	2·2725	1·14458	1·4980	0·34090	—	0·33550	—
1·1313	2·2915	1·14326	1·4986	0·34406	92·6	0·33545	49·5
1·7447	2·3017	1·14255	1·4989	0·34574	92·3	0·33542	49·4
2·3942	2·3125	1·14180	1·4992	0·34750	92·1	0·33542	49·6
3·0243	2·3233	1·14106	1·4997	0·34926	92·1	0·33543	49·7
3·6502	2·3340	1·14032	1·5000	0·35099	92·1	0·33540	49·6
			Aminodurene in dioxan.				
0·0000	2·2040	0·97280	1·4200	0·27860	—	0·24618	—
1·0580	2·2285	0·97317	1·4216	0·28273	99·9	0·24710	49·8
2·2988	2·2578	0·97353	1·4234	0·28759	99·9	0·24812	49·3
3·3422	2·2826	0·97394	1·4250	0·29172	100·1	0·24905	49·6
4·0675	2·3000	0·97425	1·4261	0·29454	100·0	0·24968	49·6
			Methylmesidine in benzene.				
0·0000	2·2725	1·14460	1·4980	0·34090	—	0·33550	—
0·8998	2·2826	1·14394	1·4982	0·34260	79·0	0·33543	48·9
1·4678	2·2887	1·14353	1·4983	0·34363	78·4	0·33538	48·8
1·9701	2·2946	1·41322	1·4984	0·34462	79·1	0·33533	48·8
3·2848	2·3095	1·14228	1·4987	0·34710	79·1	0·33522	48·8
5·2360	2·3322	1·14082	1·4991	0·35081	79·1	0·33502	48·7
			Methylmesidine in dioxan.				
0·0000	2·2050	0·97286	1·4200	0·27879	—	0·24619	—
0·8247	2·2172	0·97370	1·4210	0·28104	82·3	0·24691	49·7
1·6415	2·2294	0·97455	1·4219	0·28326	82·3	0·24758	49·4
2·3728	2·2406	0·97526	1·4228	0·28531	82·6	0·24825	49·7
3·0135	2·2500	0·97587	1·4236	0·28702	82·4	0·24880	49·6
5·6023	2·2888	0·97855	1·4265	0·29406	82·3	0·25104	49·6

TABLE 2.

	$10^3\alpha$	$10^4\beta$	$10^3\nu$	$P_{2\infty}$ (c.c.)	$[R_D]$ (c.c.)	μ (D)	μ' (D)
Mesidine in benzene	1800	−980	139	88·0	45·0	1·45	1·41
Mesidine in dioxan	2504	642	411	96·1	45·5	1·57	1·53
Aminodurene in benzene	1665	−1165	164	92·4	49·6	1·45	1·41
Aminodurene in dioxan	2315	343	427	100·1	49·6	1·57	1·53
Methylmesidine in benzene ...	1110	−712	63	79·1	48·8	1·22	1·17
Methylmesidine in dioxan ...	1495	1013	336	82·3	49·6	1·26	1·22

TABLE 3.

	$P_{2\infty}$ (c.c.) in:		μ (D) in:			
	benzene	dioxan	benzene	dioxan	ΔP (c.c.)	$\Delta\mu$ (D)
Aniline [1]	78·3	95·1	1·53	1·77	16·8	0·24
Mesidine [4]	88·0	96·1	1·45	1·57	8·1	0·12
Aminodurene [4]	92·4	100·1	1·45	1·57	7·7	0·12
2 : 4 : 6-Tribromoaniline [2]	116·7	139·5	1·73	2·00	22·8	0·27
n-Butylamine [2]	61·1	60·1	1·34	1·33	−1·0	−0·01
Methylaniline [1]	93·2	106·7	1·68	1·86	13·5	0·18
Diphenylamine [3]	81·2	94·2	1·08	1·32	13·0	0·24
Methylmesidine [4]	79·1	82·3	1·22	1·26	3·2	0·04
Dimethylamine [4]	43·3	—	1·17	—	—	—
Dimethylaniline [1]	94·1	97·8	1·61	1·66	3·7	0·05

[1] Part I. [2] Part II. [3] Part IV. [4] This paper. [5] Le Fèvre and Russell, *Trans. Faraday Soc.*, 1947, **43**, 374.

in which, for convenience, all the moments quoted are calculated on the assumption that $P_{E+A} = [R_D]$. In dioxan solution the apparent dipole moments of mesidine and aminodurene are each 0·12 D higher than in benzene solution, but this difference is less than was found for aniline or 2 : 4 : 6-tribromoaniline.

On the other hand, the dipole moment of methylmesidine in benzene is very much lower than that of methylaniline, and very little higher than that of dimethylamine, suggesting that in this compound resonance is almost completely suppressed sterically, as has been found with dimethylmesidine (Ingham and Hampson, *loc. cit.*) and 2 : 4 : 6-tribromodimethylaniline (Part II, *loc. cit.*). Further, the apparent moment of methylmesidine in dioxan solution is only 0·04 D greater than in benzene. As there is no *a priori* reason to believe that the tendency towards hydrogen bonding should be so much less than for methylaniline it would appear that the increase in apparent moment accompanying hydrogen bonding in these amines is intimately associated with the mesomeric effect of the amine molecule. This observation, therefore, supports the view (Part IV) that a large increase in molecular polarisation and consequently in apparent dipole moment accompanies hydrogen bonding only when a large increase in the mesomeric effect can occur. When such is impossible, as with alkylamines in dioxan, no abnormality in the apparent dipole moment is observed. These results suggest, in fact, that comparative polarisation measurements in benzene and dioxan solutions could be used to test for the existence or otherwise of a mesomeric effect in amines, phenols, and other proton-donor molecules which are too complex to permit the satisfactory interpretation of their dipole moments in benzene alone.

For methylmesidine the difference between the apparent moments in dioxan and benzene solutions is approximately the same as for dimethylaniline, and hence may be attributed to a normal solvent effect, although the possibility that it is due to an increase in a small mesomeric effect in the methylmesidine molecule cannot be excluded. Although it is impossible on steric grounds for the methylamino-group to become coplanar with the ring, it has been realised to an increasing extent recently that appreciable π-bonding can occur, for instance between the two ring systems of derivatives of diphenyl, even when the planes of the two rings are inclined at a considerable angle to one another (Guy, *J. Chim. phys.*, 1949, **46**, 469; Beaven, Hall, Lesslie, and Turner, *J.*, 1952, 854).

This view lends particular interest to the apparent dipole moments of mesidine and aminodurene in the two solvents. As pointed out by Hampson and his co-workers, the values in benzene solution suggest that the contribution of the mesomeric form is less than for aniline, and this conclusion is supported by the relatively smaller increases in apparent dipole moment observed in dioxan solution. One of the problems remaining to be solved, however, is the difference in behaviour of mesidine as compared with 2 : 4 : 6-tribromoaniline, for which the moment in benzene is appreciably greater than that of aniline and for which the moment in dioxan is increased almost proportionately to that of aniline. In Part II it was suggested that the $-I$ effects of the bromine atoms favoured the double-bonded structure and therefore caused the moment to be greater than that of aniline. However, in view of the results with mesidine and aminodurene it would have been expected that the bromine atoms, being only slightly smaller than the methyl group, would have had at least some slight effect in inhibiting the mesomeric effect.

Possible reasons for this difference in behaviour include: (i) Mutual repulsion of the hydrogen atoms. (ii) Displacement of the C–X bonds in the trisubstituted compounds from their symmetrical positions: a slight effect of this type would increase considerably the dipole moment of a symmetrical trihalogenoaniline but would have little effect for mesidine, in which the corresponding group moments are smaller; if this were the cause, however, it would not be expected that the difference between the moments in dioxan and in benzene would be more than twice as great for 2 : 4 : 6-tribromoaniline as for mesidine. (iii) Formation of hydrogen bonds between the methyl groups and nitrogen atoms in mesidine and aminodurene (Watson, *Ann. Reports*, 1939, **36**, 219); this may occur with amines, but the extension of this view to embrace hydrogen bonding between methyl groups and the oxygen atoms of a nitro-group seems improbable, as (*a*) this would be

expected to increase the mesomeric effect in nitromesitylene and nitrodurene rather than decrease it, and (*b*) if this form of hydrogen bonding occurred one would expect similar bonding between the amino-hydrogen atom of diphenylamine and the oxygen atoms of nitrobenzene; no increase of polarisation arising from such cause could be detected (Part IV).

It is noteworthy that, in benzene solution, acetophenone has a dipole moment of 2·88 D, whereas the moments of acetylmesitylene and aminodurene are 2·71 and 2·68 D, respectively, indicating that in the last two compounds mesomerism is suppressed (Kadesch and Weller, *J. Amer. Chem. Soc.*, 1941, **63**, 1310). This view is supported by the higher Raman C=O frequency of acetylmesitylene and aminodurene (1699 cm.$^{-1}$) as compared with acetophenone (1684 cm.$^{-1}$) (Saunders, Murray, and Cleveland, *ibid.*, p. 3121; 1942, **64**, 1181). On the other hand, the dipole moment of mesitaldehyde (2·96 D) is actually greater than that of benzaldehyde (2·92 D) and much greater than the moments of aliphatic aldehydes (~2·5 D), suggesting that in this case there is no steric inhibition of resonance; this is confirmed by the fact that the C=O frequency of mesitaldehyde is 1687 cm.$^{-1}$.

It seems unlikely that the coplanarity of the amino-group with the ring should be inhibited by *o*-methyl groups on purely spatial grounds, whereas that of the aldehyde group is not. In extension of Watson's suggestion, weak hydrogen bonding of the methyl hydrogen atoms to the oxygen atom of the aldehyde group would be at least as possible as bonding to the nitrogen atom of an amino-group, and this would tend to increase the mesomeric effect. In the absence of proof of the formation of hydrogen bonds by methyl groups, however, this problem must remain open.

My thanks are offered to Imperial Chemical Industries Limited for the loan of a precision variable air condenser, and to Professor E. E. Turner, F.R.S., and Dr. D. M. Hall for valuable discussions.

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20. *The Mechanisms of the Thermal Decompositions of* 1 : 4-*Dichlorobutane and* 1 : 1 : 2-*Trichloroethane.*

By R. J. Williams.

1 : 4-Dichlorobutane decomposes at 673—727° K by a first-order reaction to form hydrogen chloride and butadiene (the dimerisation of which is relatively slow). The rate constant is represented by $k = 10^{14\cdot36}e^{-56,500/RT}$ sec.$^{-1}$. Reasonably reproducible induction periods were observed, the rate constants increasing and the induction periods decreasing with increase of pressure, both becoming sensibly constant above 60 mm. (initial). Propylene inhibits the reaction, extending the induction periods and diminishing the rate constants.

With 1 : 1 : 2-trichloroethane the reaction at 715° K is of the first order, exhibits induction periods, and is strongly inhibited by small amounts of propylene. It is concluded that these decompositions proceed by radical-chain reactions.

In a series of papers (Barton, Head, Howlett, Onyon, and Williams, *J.*, 1949, **148**, 155, 165; *Trans. Faraday Soc.*, 1949, **45**, 725, 735; 1950, **46**, 114; *J. Amer. Chem. Soc.*, 1950, **72**, 988; *J.*, 1951, 2033, 2039; 1952, 453) the thermal dehydrochlorination of a number of saturated aliphatic chlorinated hydrocarbons has been described. The resultant olefins or chlorinated olefins are relatively stable under the experimental conditions. Three mechanisms have been recognised for these pyrolyses: (i) heterogeneous decomposition on the clean glass surface, (ii) homogeneous unimolecular decomposition, and (iii) homogeneous radical chain decomposition. Of these (i), which is much faster than (ii) or (iii), appears to be of universal application but can be largely suppressed by deposition of a carbonaceous film on the surface owing to polymerisation and cracking of the products.

Homogeneous decomposition will proceed by a radical chain decomposition provided that neither the products of the reaction nor the reactant itself is capable of acting as an efficient inhibitor for the radical chains. Inhibition by the products is experienced if they possess allylic hydrogen atoms (*e.g.*, propene, butene) and by the reactant if the direction of radical chlorination is such that β-chloro-radicals (which readily lose a chlorine atom to continue the chain) are not formed or are formed in insufficient proportions (see, especially Barton, Head, and Williams, *J.*, 1951, 2039).

In order further to confirm these statements, the thermal decompositions of 1 : 1 : 2-trichloroethane and 1 : 4-dichlorobutane have now been investigated.

Experimental

Materials.—Commercial 1 : 4-dichlorobutane, purified as described for *n*-propyl chloride (Barton, Head, and Williams, *loc. cit.*) and fractionally distilled under reduced pressure, had b. p. 153·9° (corr.)/760 mm. (153·5°, Rust and Vaughan, *J. Org. Chem.*, 1941, **6**, 479; 155·0°, Mumford and Phillips, *J.*, 1950, 75), f. p. (SO_2 vapour-pressure thermometer) −37·3°, d_4^{12} 1·1498 (mean 1·1496, interpolated from d_4^1 1·1612, d_4^{35} 1·1340, d_4^{40} 1·1175, Heston, Hennelly, and Smyth, *J. Amer. Chem. Soc.*, 1950, **72**, 2071; d_4^{20} 1·1408, d_4^{25} 1·1353, Mumford and Phillips, *loc. cit.*), n_D^{21} 1·4559 (n_D^{25} 1·4530, Heston *et al.*, *loc. cit.*; n_D^{20} 1·4549, Mumford and Phillips, *loc. cit.*).

Commercial 1 : 1 : 2-trichloroethane, purified by the method used for 1 : 1 : 1-trichloroethane by Barton and Onyon (*J. Amer. Chem. Soc.*, 1950, **72**, 988), had b. p. 113·5° (corr.)/760 mm. (114·1°, Mumford and Phillips, *loc. cit.*; 113·67°, Dreisbach and Martin, *Ind. Eng. Chem.*, 1949, **41**, 2875; 113·5°, Timmermans, *Bull. Soc. chim. Belg.*, 1913, **27**, 334; 113·65°, Lecat, "Tables Azeotropiques," Brussels, 1949), f. p. (SO_2 vapour-pressure thermometer) −36·6° (−36·57°, Dreisbach and Martin, *loc. cit.*; −36·65°, Timmermans, *loc. cit.*; −37·4°, Henne and Hubbard, *J. Amer. Chem. Soc.*, 1936, **58**, 404), d_4^{12} 1·4445 (1·4480, extrapolated from d_4^{20} 1·4395, d_4^{25} 1·4319, Dreisbach and Martin, *loc. cit.*; d_4^{20} 1·4424, d_4^{25} 1·4355, Mumford and Phillips, *loc. cit.*; d_4^{20} 1·4411, Henne and Hubbard, *loc. cit.*).

Apparatus.—The apparatus and technique were those described by Barton and Howlett (*J.*, 1949, 155). Owing to the relatively low vapour pressures involved all external tubing was electrically heated to *ca.* 160°. Results are for reactors in which the heterogeneous decomposition had been suppressed by a carbonaceous coating and the kinetics were elucidated by following the pressure increase at constant volume.

Results

Stoicheiometry.—The reaction with 1 : 4-dichlorobutane was assumed to be $Cl{\cdot}[CH_2]_4{\cdot}Cl = CH_2{:}CH{\cdot}CH{:}CH_2 + 2HCl$ by analogy with that of 2 : 2′-dichlorodiethyl ether (Barton, Head, and Williams, *loc. cit.*). This view was supported by some long-term runs in which it was found that 40-mm. initial pressure of reactant trebled its pressure in 18 hours at 695—727° K. In view of the known polymerisation of butadiene at these temperatures this was fortuitous but it was found that 40-mm. initial pressure of butadiene under the same conditions first decreased and then increased to a steady value within 2% of the original pressure. These facts taken together indicate that two molecules of hydrogen chloride are eliminated. Calculations based on Rowley and Steiner's results (*Discuss. Faraday Soc.*, 1951, **10**, 198) showed that the dimerisation of butadiene could be neglected over the first portion of the decomposition, for initial pressures of reactant less than 50 mm.

1 : 1 : 2-Trichloroethane was assumed to decompose analogously to 1 : 1 : 1-trichloroethane (Barton and Onyon, *loc. cit.*) and, indeed, overnight pressure ratios at 714° K were found to be identical (2·5).

Kinetics.—1 : 4-Dichlorobutane was found to decompose by a first-order process. Temperature-dependent induction periods were noted, similar to those with 2 : 2′-dichlorodiethyl ether. The induction periods decreased and the rate constants increased with increasing initial pressure but both became sensibly constant above about 60 mm. initial pressure. The rate constants, for initial pressures of 40 mm., were given by $k = 10^{14\cdot36}e^{-56,500/RT}$ sec.$^{-1}$ and the variation of the induction periods (except at the highest temperature where errors in measurement are relatively larger) could be represented by the expression $I = 10^{-16\cdot5}e^{54,700/RT}$min. In accordance with previous custom no error limits are given for these constants for the chain reaction. The data are summarised in Table 1 which includes values for the rate constants and induction periods calculated from the above equations.

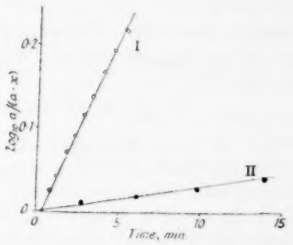
TABLE 1. *Unpacked reactor; initial pressure, 40 mm.*

Temp. (K)	No. of runs	Mean 10^3k (sec.$^{-1}$)	Standard error of mean k * (%)	$10^3k_{calc.}$ (sec.$^{-1}$)	Mean induction period (I), sec.	Standard error of mean I * (%)	$I_{calc.}$ (sec.)
673·0°	6	0·104	0·6	0·102	1036	2	1092
683·5	5	0·200	0·8	0·200	728	2	586
687·5	3	0·256	0·8	0·257	518	4	466
695·0	14	0·404	1·1	0·389	308	2	301
704·0	6	0·645	0·6	0·660	191	4	181
710·5	4	0·99	1·1	0·96	133	4	125
715·0	7	1·30	1·0	1·23	102	3	100
727·0	12	2·38	1·0	2·40	31	4	—

* Given by $\frac{100}{\bar{x}}\sqrt{\frac{\Sigma(x-\bar{x})^2}{n(n-1)}}$ where the symbols have the usual significance.

Addition of propylene, which is diagnostic for radical chains in these decompositions, prolonged the induction periods and considerably reduced the final rate. Both effects increased

I, *Without propylene.*
II, *With propylene at* 715°K.



rapidly with the proportion of propylene (to about 4%) after which only a slow increase was noted. The data are summarised in Table 2.

In contrast to the above results 1 : 1 : 2-trichloroethane gave poor reproducibility and was not suited to detailed kinetic analysis. This was almost certainly due to the inhibiting effect of products noted by Barton and Onyon (*loc. cit.*) in the pyrolysis of 1 : 1 : 1-trichloroethane.

TABLE 2. *Unpacked reactor at* 712° K.

p_0, mm. of $C_4H_8Cl_2$	p, mm. C_3H_8	100 p/p_0	Mean 10^3k (sec.$^{-1}$)	Induction period (sec.)
Mean	—	—	1·02	118
41·3	0·1	0·25	0·76	135
40·6	0·2	0·5	0·69	155
40·6	0·4	1·0	0·51	186
40·8	1·6	4·0	0·42	260
40·8	4·2	10·5	0·35	270
40·6	16·3	40·8	0·30	320

Over 100 kinetic runs were carried out, a typical example (initial pressure 60 mm.; temp. 714° K) being depicted in the Figure. In each case the kinetics were of the first order and induction periods were observed. Addition of 2·5% of propylene reduced the rate constant 18-fold as shown by the lower line in the Figure where the elimination of the induction period can also be seen.

DISCUSSION

Both the above decompositions exhibit as their main features temperature-dependent induction periods and positive inhibition by small quantities of propylene. These features are the same as for 1 : 2-dichloroethane, 1 : 1 : 1-trichloroethane, both tetrachloroethanes, and 2 : 2′-dichlorodiethyl ether (Barton *et al.*, *loc. cit.*) and clearly indicate the essential radical-chain nature of the decompositions.

The results accord with theory for 1 : 1 : 2-trichloroethane, as radical chlorination must yield a β-chloro-radical, $CHCl_2{\cdot}\dot{C}HCl$ or $\dot{C}Cl_2{\cdot}CH_2Cl$, capable of readily eliminating a chlorine atom to continue the chain, simultaneously forming chlorinated ethylenes. From previous studies (Barton and Onyon, *loc. cit.*) it is known that chlorinated ethylenes are only feebly inhibitory.

In the case of 1 : 4-dichlorobutane the radical-chain reaction detected implies that radical chlorination must take place largely at the 2-position, a directive effect in accord with the principles proposed by Ash and Brown ("Records of Chemical Progress," 1948, p. 81). Since however some attack will occur at the 1-position, leading to "dead" radicals incapable of readily losing a chlorine atom, the radical chains cannot be expected to be long. This is supported qualitatively by the results of addition of propylene which produced proportionately a far lower retardation of rate than in the case of 1 : 1 : 2-trichlorethane, indicating that non-chain processes must also be of considerable importance Lack of inhibition by the product, butadiene, is comparable to the case of ethylene, already shown to be a poor inhibitor (Barton and Howlett, *loc. cit.*).

I am indebted to Dr. D. H. R. Barton for helpful discussions during this work which was carried out during the tenure of a Courtaulds' Postgraduate Scholarship.

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21. *Experiments on the Preparation of Indolocarbazoles. Part V.* The Synthesis of Indolo(3′ : 2′-1 : 2)carbazole and its 3-Methyl Derivative.*

By J. A. HALL and S. G. P. PLANT.

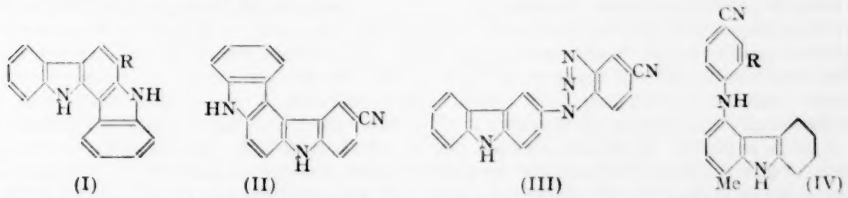
Indolo(3′ : 2′-1 : 2)carbazole and its 3-methyl derivative have been synthesised through their octahydro-compounds by heatng 2-chloro*cyclo*hexanone with 5-amino- and 5-amino-8-methyl-tetrahydrocarbazole respectively. The preparation of certain derivatives of 5- and 8-anilinotetrahydrocarbazole which might serve for the unambiguous synthesis of substituted indolocarbazoles has been studied.

THE well-known reaction by which indoles are obtained from aromatic amines and 2-halogeno-ketones (see, *e.g.*, Möhlau, *Ber.*, 1881, **14**, 173; 1882, **15**, 2480; Bischler, *Ber.*, 1892, **25**, 2860) has been extended to the preparation of tetrahydrocarbazole ("tetrahydrocarbazole" throughout this communication signifies 1 : 2 : 3 : 4-tetrahydrocarbazole) from aniline and 2-chloro*cyclo*hexanone (D.R.-P. 374,098; *Chem. Zentr.*, 1923, IV, 724). Several substituted tetrahydrocarbazoles have been prepared in this way by Campbell and McCall (*J.*, 1950, 2870) in yields which were generally 30—60%. It seemed possible therefore that this reaction might be applied to the aminotetrahydrocarbazoles with the formation of octahydroindolocarbazoles from which the parent substances would be formed on dehydrogenation. The only one of the five isomeric indolocarbazoles so far prepared is the substance obtained by Tomlinson (*J.*, 1951, 809) by dehydrogenation of the product obtained by applying the Fischer indole synthesis to bis*cyclo*hexanone *m*-phenylenedihydrazone, and regarded as indolo(3′ : 2′-1 : 2)carbazole (I; R = H), although two structural interpretations are possible.

The material obtained by heating 5-aminotetrahydrocarbazole with 2-chloro*cyclo*hexanone has yielded a small quantity of 5 : 6 : 7 : 8 : 4′ : 5′ : 6′ : 7′-octahydroindolo(3′ : 2′-1 : 2)carbazole which gave, on dehydrogenation, indolo(3′ : 2′-1 : 2)carbazole, identical with Tomlinson's substance, the structure of which is thus unambiguously established. Similar treatment of 5-aminotetrahydro-8-methylcarbazole has given a compound which, in view of its ultra-violet absorption spectrum (see Figure), must be 3-methylindolo(3′ : 2′-1 : 2)carbazole (I; R = Me). The yields of these indolocarbazoles were very small, and attempts to obtain isomers of the former from 6-, 7-, and 8-aminotetrahydrocarbazole failed. When 2-arylamino-ketones are heated with aromatic amines, indoles derived from the amine are formed with elimination of the arylamino-group (Bischler, *loc. cit.*), and Campbell and McCall (*loc. cit.*) have observed that 2-*p*-bromoanilino*cyclo*hexanone gives tetrahydrocarbazole (in unstated yield) when heated with aniline hydrochloride. It seemed possible that by heating the last-named ketone with 5-aminotetrahydrocarbazole

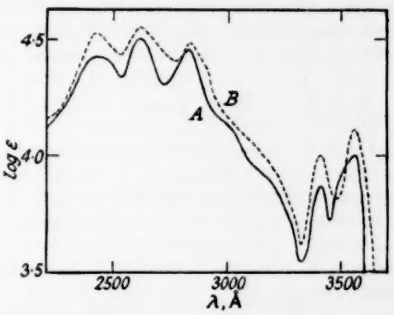
* Part IV, *J.*, 1951, 809.

hydrochloride better yields of the indolocarbazole would be obtained, but nothing crystalline was isolated from the product.



(I) (II) (III) (IV)

Clifton and Plant (*J.*, 1951, 461) obtained a substance regarded as 6-cyanoindolo(2′ : 3′-3 : 4)carbazole (II) by applying the Graebe–Ullmann reaction to the triazole (III), prepared from 3-aminocarbazole. This suggests that indolocarbazole derivatives of unambiguous structure might be obtained fairly readily from 5- and 8-aminotetrahydrocarbazole and some of their substitution products through suitable triazoles. These amines are more easily accessible than the corresponding aminocarbazoles. So the condensation of 5- and 8-amino-, 5-amino-8-chloro-, and 5-amino-8-methyl-tetrahydrocarbazole with 1-chloro-2 : 4-dinitrobenzene, 4-chloro-3-nitrobenzonitrile, and/or 4-bromo-3-nitroacetophenone was studied under a variety of conditions. The yields of the substituted anilinotetrahydro-



A, ————, *Indolo*(3′ : 2′-1 : 2)*carbazole*.
B, – – – – –, 3-*Methylindolo*(3′ : 2′-1 : 2)*carbazole*.
(*Both in methanol solution*.)

carbazoles were generally disappointing and the products difficult to purify, owing mainly to the relative instability of the initial amines under the reaction conditions. Of the derivatives examined, 5-(4-cyano-2-nitroanilino)tetrahydro-8-methylcarbazole (IV; R = NO_2) was obtained most readily in reasonable amount; it was reduced to the amine (IV; R = NH_2), but attempts to make the corresponding triazole failed. Clifton and Plant (*loc. cit.*) found it necessary to use a carefully controlled amount of nitrous acid in preparing the triazole (III) in order to avoid other reactions, and the possibilities of such complications are even greater with the compound (IV; R = NH_2) owing to the presence of a reactive double bond.

Experimental

8-*Chlorotetrahydro-5-nitrocarbazole*.—The following method for the preparation of this substance gave a better yield than that of Perkin and Plant (*J.*, 1921, **119**, 1825). After a mixture of 2-chloro-5-nitrophenylhydrazine (15 g.), *cyclo*hexanone (8 c.c.), and a little ethanol had been boiled for a few minutes, acetic acid (80 c.c.) and concentrated hydrochloric acid (20 c.c.) were added, and the whole was refluxed for 2 hours. The product which separated on cooling was obtained from acetic acid in orange-yellow needles (12 g.), m. p. 214°.

5-*Aminotetrahydrocarbazole*.—Reduction of 8-chlorotetrahydro-5-nitrocarbazole to a mixture of 5-aminotetrahydro- and 5-aminohexahydro-carbazole has been described by Plant (*J.*, 1936, 899). The following modified procedure has worked well for the preparation of the tetrahydro-base. After a mixture of 8-chlorotetrahydro-5-nitrocarbazole (30 g.), granulated tin (125 g.), ethanol (250 c.c.), and concentrated hydrochloric acid (250 c.c.) had been refluxed for 1½ hours, the solution was filtered, the ethanol distilled off, and the residue made strongly alkaline with aqueous sodium hydroxide. The precipitated solid was dried and extracted with hot benzene.

When the extract was concentrated, 5-aminotetrahydrocarbazole (13·2 g.) separated, on cooling, in colourless prisms, m. p. 162—164°.

Indolo(3′ : 2′-1 : 2)*carbazole.*—After a mixture of 5-aminotetrahydrocarbazole (2·25 g.) and 2-chloro*cyclo*hexanone (0·75 g.) had been heated at 160° for ½ hour, the cold material was powdered and extracted with dilute hydrochloric acid. The residue was dried and extracted with boiling benzene, the solvent being then removed from the filtered extract by distillation under reduced pressure. 5 : 6 : 7 : 8: 4′ : 5′ : 6′ : 7′-Octahydroindolo(3′ : 2′-1 : 2)carbazole was obtained in nearly colourless prisms (0·05 g.), m. p. 225—227° (from acetic acid) (Tomlinson, *loc. cit.*, gives m. p. 228°). This substance was heated with half its bulk of palladium–charcoal, first at 240° for 20 minutes and then at 320° for ½ hour, under nitrogen. Indolo(3′ : 2′-1 : 2)carbazole sublimed as colourless plates, m. p. 299—300°, not depressed by admixture with a specimen obtained from bis*cyclo*hexanone *m*-phenylenedihydrazone and kindly supplied by Dr. M. L. Tomlinson. A further quantity was obtained by extraction from the residue with acetic acid, precipitation with water, and sublimation in nitrogen.

5-Aminotetrahydro-8-methylcarbazole.—Prepared from diazotised 4-nitro-*o*-toluidine by stannous chloride in hydrochloric acid, *4-nitro-o-tolylhydrazine* (yield, 50%) crystallised from methanol in yellow needles, m. p. 154° (Found : C, 50·2; H, 5·4. $C_7H_9O_2N_3$ requires C, 50·3; H, 5·4%). It was converted into *tetrahydro-8-methyl-5-nitrocarbazole* (yield, 60%), orange prisms, m. p. 215° (from acetic acid), as described above for the analogous 8-chloro-compound except that the cyclisation was effected at 100° (Found : C, 67·9; H, 6·2; N, 11·9. $C_{13}H_{14}O_2N_2$ requires C, 67·8; H, 6·1; N, 12·2%). Sodium hydrosulphite (dithionite) was gradually added to a solution of the nitro-compound (10 g.) in the minimum amount of boiling aqueous ethanol (75% v/v) until the colour became very pale yellow. The ethanol was distilled off, water added, and the solid *5-aminotetrahydro-8-methylcarbazole* (6·5 g.) crystallised from benzene, from which it separated in colourless plates, m. p. 202—204° (rapid heating) (Found : C, 77·6; H, 7·8. $C_{13}H_{16}N_2$ requires C, 78·0; H, 8·0%).

3-Methylindolo(3′ : 2′-1 : 2)*carbazole.*—5-Aminotetrahydro-8-methylcarbazole (2·1 g.) was heated with 2-chloro*cyclo*hexanone (0·75 g.) for 5 minutes at 160°, cooled, and ground with dilute hydrochloric acid. The insoluble material was dried, and extracted with hot benzene, the solvent being distilled from the extract under reduced pressure. The residue was heated with its own volume of palladium–charcoal in nitrogen at 240° for 20 minutes. The temperature was then gradually raised to 320° and kept there for 2½ hours. When the solid which sublimed was resublimed in nitrogen at 270°, *3-methylindolo*(3′ : 2′-1 : 2)*carbazole* was obtained in colourless needles (0·01 g.), m. p. 261—262° (Found : C, 85·3; H, 5·2. $C_{19}H_{14}N_2$ requires C, 84·4; H, 5·2%).

5-Amino-8-chlorotetrahydrocarbazole.—8-Chlorotetrahydro-5-nitrocarbazole was reduced as described above for the analogous 8-methyl compound, and the *amine* (yield, 65%) isolated from light petroleum (b. p. 60—80°) in colourless prisms, decomp. above 160° without melting (Found : C, 65·0; H, 5·7. $C_{12}H_{13}N_2Cl$ requires C, 65·3; H, 5·9%). *5-Acetamido-8-chlorotetrahydrocarbazole*, colourless needles, m. p. 236° (from benzene), separated after the amine had been boiled with a slight excess of acetic anhydride in benzene (Found : N, 10·6. $C_{14}H_{15}ON_2Cl$ requires N, 10·7%).

Derivatives of 5-Anilinotetrahydrocarbazole.—(*a*) After a mixture of 5-aminotetrahydrocarbazole (0·2 g.), 1-chloro-2 : 4-dinitrobenzene (0·3 g.), and anhydrous sodium acetate (0·2 g.) had been heated on a steam-bath for an hour, cooled, and extracted with hot acetic acid, the addition of water to the filtered extract precipitated *5-(2 : 4-dinitroanilino)tetrahydrocarbazole*, red prisms (0·06 g.), m. p. 224° (from ethanol) (Found : C, 61·0; H, 4·9. $C_{18}H_{16}O_4N_4$ requires C, 61·4; H, 4·5%). (*b*) The amine (0·65 g.), 4-chloro-3-nitrobenzonitrile (0·65 g.), and anhydrous sodium acetate (0·5 g.) were heated at 160° for ½ hour, and the product extracted with hot benzene. After the extract had been concentrated, the solute was adsorbed on alumina and then thrice recrystallised from ethanol; *5-(4-cyano-2-nitroanilino)tetrahydrocarbazole* was obtained in red prisms (0·1 g.), m. p. 214—216° (Found : C, 68·1; H, 4·8. $C_{19}H_{16}O_2N_4$ requires C, 68·7; H, 4·8%). (*c*) Prepared from 4-bromo-3-nitroacetophenone as described for the analogous cyano-compound, *5-(4-acetyl-2-nitroanilino)tetrahydrocarbazole* (yield, 30%) crystallised from ethanol in red prisms, m. p. 181° (Found : C, 68·8; H, 5·6. $C_{20}H_{19}O_3N_3$ requires C, 68·8; H, 5·4%).

Derivatives of 5-Anilino-8-chlorotetrahydrocarbazole.—(*a*) After 5-amino-8-chlorotetrahydrocarbazole (0·45 g.) had been heated with 1-chloro-2 : 4-dinitrobenzene (0·45 g.) and anhydrous sodium acetate (0·2 g.) at 130—135° for ¾ hour, and the product extracted with boiling ethanol (5 × 50 c.c.), the material obtained by pouring the extracts into water was dried and purified

by adsorption from benzene on alumina. 8-*Chloro*-5-(2 : 4-*dinitroanilino*)*tetrahydrocarbazole* was obtained in red needles (0·01 g.), m. p. 282° (from benzene) (Found : C, 56·2; H, 3·8. $C_{18}H_{15}O_4N_4Cl$ requires C, 55·9; H, 3·9%). (*b*) An intimate mixture of 5-amino-8-chlorotetrahydrocarbazole hydrochloride (1 g.; prepared by passing hydrogen chloride through the base in ether), 4-chloro-3-nitrobenzonitrile (0·75 g.), and sodium acetate (2 g.) was refluxed in amyl alcohol for 2½ hours, the solvent removed under reduced pressure, and the product extracted from the residue with boiling benzene. After purification by adsorption on alumina, 8-*chloro*-5-(4-*cyano*-2-*nitroanilino*)*tetrahydrocarbazole* crystallised from acetic acid in red needles (0·1 g.), m. p. 292° (Found : C, 62·6; H, 4·1. $C_{19}H_{15}O_2N_4Cl$ requires C, 62·2; H, 4·1%).

Derivatives of 5-*Anilinotetrahydro*-8-*methylcarbazole.*—(*a*) 5-Aminotetrahydro-8-methylcarbazole (0·5 g.), 1-chloro-2 : 4-dinitrobenzene (0·5 g.), and anhydrous sodium acetate (0·3 g.) were heated on a steam-bath for 2 hours, cooled, and ground with a little ethanol. 5-(2 : 4-*Dinitroanilino*)*tetrahydro*-8-*methylcarbazole*, red needles (0·45 g.; from ethanol), m. p. 258°, remained (Found : C, 62·2; H, 5·2. $C_{19}H_{18}O_4N_4$ requires C, 62·3; H, 4·9%).

(*b*) Prepared similarly from 4-chloro-3-nitrobenzonitrile, 5-(4-*cyano*-2-*nitroanilino*)*tetrahydro*-8-*methylcarbazole* crystallised from ethanol in red needles (yield, 60%), m. p. 267° (Found : C, 69·2; H, 5·2. $C_{20}H_{18}O_2N_4$ requires C, 69·4; H, 5·2%). After its solution in dioxan–water (3 : 2 by volume) had been treated on the steam-bath with sodium dithionite until almost colourless, water precipitated 5-(2-*amino*-4-*cyanoanilino*)*tetrahydro*-8-*methylcarbazole* (33%), pale brown needles (from aqueous methanol), m. p. 187—189° (Found : C, 75·8; H, 6·3. $C_{20}H_{20}N_4$ requires C, 75·9; H, 6·3%).

8-(2 : 4-*Dinitroanilino*)*tetrahydrocarbazole.*—Prepared like the isomeric 5-(2 : 4-dinitroanilino)-compound described above, this *compound* was extracted from the reaction mixture with boiling benzene, purified on alumina, and twice recrystallised from ethanol; it formed red prisms (yield, 20%), m. p. 191—193° (Found : C, 61·4; H, 4·6%).

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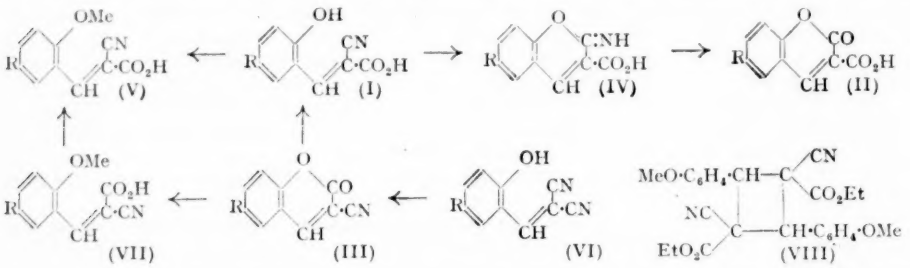
22. *Stereochemistry of Arylidenecyanoacetic Acids and Arylarylideneacetonitriles.*

By WILSON BAKER and C. S. HOWES.

Aromatic aldehydes react with the sodium salt or the ethyl ester of cyanoacetic acid to give *trans*(with respect to the aryl and carboxyl groups)-arylidenecyanoacetic acids or esters. In the *o*-hydroxyaryl series, the configuration is established by conversion in boiling water into coumarin-3-carboxylic acids (II). *cis*-2-Methoxyarylidenecyanoacetic acids are prepared by methylation in alkaline solution of 3-cyanocoumarins (III) (new preparation). Two stereoisomeric pairs of 2-methoxyarylidenecyanoacetic acids have thus been prepared; the *cis*-acids are converted into the *trans*-acids on melting. In the light of this work the arylarylideneacetonitriles are shown to be the *trans*-isomers.

2-HYDROXYBENZYLIDENECYANOACETIC ACID (I; R = H), prepared by condensation of salicylaldehyde with aqueous, alkaline sodium cyanoacetate, passes in 1—2 minutes in boiling water into the ammonium salt of coumarin-3-carboxylic acid (II; R = H) (Baker and Lapworth, *J.*, 1925, **127**, 561; see also Clarke and Francis, *Ber.*, 1911, **44**, 275). This cannot be due to hydrolysis of the cyano- to a carboxyl group and lactonisation (Bechert, *J. pr. Chem.*, 1894, **50**, 11), since the arylidenecyanoacetic acids, except those with an *o*-hydroxyl group, are unaffected by prolonged boiling with water or even hydrochloric acid, nor can it be due to lactonisation to 3-cyanocoumarin (III; R = H) and hydrolysis to the acid (II; R = H), since (III; R = H) and the related amide are not hydrolysed by boiling water. The acid (I; R = H) must, therefore, pass into (II; R = H) *via* an imino-lactone (IV; R = H) which is at once hydrolysed to the coumarin, and must consequently possess adjacent hydroxyl and cyano-groups. Hence (I; R = H) is a derivative of *trans*-cinnamic acid, and may be termed *trans*-2-hydroxybenzylidenecyanoacetic acid (*trans*-α-cyano-2-hydroxycinnamic acid).

The conversion of (I; R = H) into (II; R = H) is initiated by attack of the anionoid phenolic oxygen atom on the cationoid carbon of the cyano-group held in a stereochemically favourable position by the olefinic bond. The related saturated acid, 2-hydroxybenzylcyanoacetic acid, is almost unchanged by boiling with water for 30 hours. The time of



conversion of (I; R = H) into (II; R = H) in boiling water is increased by addition of hydrochloric acid (*e.g.*, 3 minutes in N-HCl, 7 minutes in 10N-HCl); the choice between alternative explanations for this behaviour cannot be made.

Evidence that an imino-lactone (IV; R = H) is an intermediate in the conversion of (I; R = H) into (II; R = H) is provided by a new preparation of 3-cyanocoumarin (III; R = H) from *o*-hydroxybenzylidenemalononitrile (VI; R = H), itself prepared from salicylaldehyde and malononitrile. The dinitrile (VI; R = H), which is insoluble in water, dissolves rapidly in cold dilute hydrochloric acid as the salt of the imino-lactone, and, after a few minutes, the neutral 3-cyanocoumarin (III; R = H) separates out. The dicyano-compound (VI; R = H) is a powerful sternutator and irritant, and thus resembles some other αβ-unsaturated malononitriles (Corson and Stoughton, *J. Amer. Chem. Soc.*, 1928, **50**, 2825).

3-Cyanocoumarin (III; R = H) dissolves in N-sodium hydroxide at 30° as the sodium salt of *cis*-2-hydroxybenzylidenecyanoacetic acid; acidification reprecipitates (III; R = H). If, however, the alkaline solution is boiled for five minutes, acidification precipitates the *trans*-acid (I; R = H). Mild treatment with methyl sulphate of the solution of the sodium salt of the *cis*-acid gives *cis*-2-methoxybenzylidenecyanoacetic acid (VII; R = H), which differs from the *trans*-2-methoxybenzylidenecyanoacetic acid (V; R = H) prepared either by methylation of the *trans*-acid (I; R = H) or by condensation of 2-methoxybenzaldehyde with aqueous sodium cyanoacetate. It was hoped that there might be sufficient difference in the ultra-violet absorption spectra of the *cis*- and the *trans*-isomer to enable them to be used as reference compounds in deciding the stereochemistry of other arylidenecyanoacetic acids or related molecules; the curves are, however, so alike (see Table) that this object cannot be achieved.

These stereoisomeric acids (VII; R = H) and (V; R = H) differ markedly in their stability, the *cis*-acid (m. p. 159—160°) being converted into the *trans*-acid (m. p. 211—212°) at its melting point. Again, although the *trans*-acid undergoes normal esterification to the ethyl ester (Dave and Nargund, *J. Univ. Bombay*, 1938, **7**, 196) (also obtained directly from *o*-methoxybenzaldehyde and ethyl cyanoacetate), the *cis*-acid, even under mild conditions in presence of hydrogen chloride or toluene-*p*-sulphonic acid, gives the ethyl ester of the *trans*-acid. The two acids also differ in their behaviour when the solids are irradiated with ultra-violet light (see Experimental).

Crystalline ethyl *trans*-2-methoxybenzylidenecyanoacetate passes extremely slowly in daylight, more rapidly in ultra-violet light, into a higher-melting, saturated dimeride. This is probably one stereoisomer of diethyl 1 : 3-dicyano-2 : 4-di-*o*-methoxyphenyl*cyclo*butane-1 : 3-dicarboxylate (VIII).

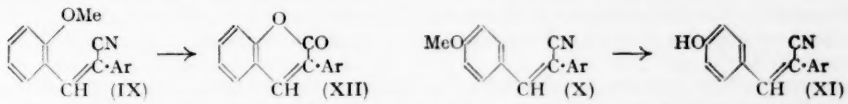
A similar series of reactions has been carried out starting with 5-bromo-2-hydroxybenzaldehyde. With sodium cyanoacetate it gives *trans*-5-bromo-2-hydroxybenzylidenecyanoacetic acid (I; R = Br), which with boiling water gives the ammonium salt of 6-bromocoumarin-3-carboxylic acid (II; R = Br). Methylation of (I; R = Br) gives

trans-5-bromo-2-methoxybenzylidenecyanoacetic acid (V; R = Br), also obtained from 5-bromo-2-methoxybenzaldehyde and sodium cyanoacetate. 5-Bromo-2-methoxybenzaldehyde and malononitrile give 5-bromo-2-hydroxybenzylidenemalononitrile (VI; R = Br), converted by dissolution in dilute hydrochloric acid into 6-bromo-3-cyanocoumarin (III; R = Br). Methylation of this cyanocoumarin in alkaline solution gives *cis*-5-bromo-2-methoxybenzylidenecyanoacetic acid (VII; R = Br). The *cis*-acid crystallises unchanged from benzene but gives the *trans*-acid when crystallised from ethanol or when melted. There were again differences in the behaviour of the solid stereoisomerides towards ultra-violet light; the ultra-violet extinction curves in ethanol were very similar, but as in the case of the stereoisomeric acids (V and VII; R = H) the absorption curve of the *trans*-acid is displaced towards the longer wave-lengths in comparison with the *cis*-acid.

Ethyl *trans*-5-bromo-2-methoxybenzylidenecyanoacetate, obtained either by esterification of the acid (I; R = Br) or, more conveniently, from 5-bromo-2-methoxybenzaldehyde and ethyl cyanoacetate, does not dimerise in ultra-violet light.

In the β-resorcylaldehyde series, 2-hydroxy-4-methoxybenzaldehyde and sodium cyanoacetate give *trans*-2-hydroxy-4-methoxybenzylidenecyanoacetic acid, converted by boiling water into 7-methoxycoumarin-3-carboxylic acid (Baker and Collis, *J.*, 1949, S 12), and by methyl sulphate and alkali into *trans*-2 : 4-dimethoxybenzylidenecyanoacetic acid, also obtained from 2 : 4-dimethoxybenzaldehyde and sodium cyanoacetate. Esterification of *trans*-2 : 4-dimethoxybenzylidenecyanoacetic acid gave the ethyl ester, identical with that obtained from 2 : 4-dimethoxybenzaldehyde and ethyl cyanoacetate (Kauffmann, *Ber.*, 1919, **52**, 1433); this ester is unaltered by ultra-violet light.

The present work explains the "abnormal behaviour" of 2-methoxybenzylidenearylacetonitriles (IX) when demethylated by boiling with pyridine hydrochloride (Buu-Hoï, Hoán, and Lavit, *J.*, 1950, 2130; Buu-Hoï and Hoán, *J.*, 1951, 251; Buu-Hoï, Hoán, and Khenissi, *J.*, 1951, 2307). These authors observed that although demethylation of, *e.g.*, 4-methoxybenzylidenearylacetonitriles (X) gave simply the phenols (XI), yet demethylation of the corresponding 2-methoxybenzylidene derivatives "resulted also in hydrolysis of the nitrile group and lactonisation, with formation of 3-substituted coumarins" (XII).



There is no reason to expect a different order of stability of the CN groups in the *o*- and *p*-methoxy-compounds (IX) and (X), and it is clear that the demethylation of (IX) is followed by reaction of the phenolic group with the adjacent cyano-group to give an imino-lactone which is then hydrolysed to the 3-arylcoumarin (XII). Hence these 2-methoxybenzylidenearylacetonitriles must possess that geometrical configuration in which the aryl radicals are in the *trans*-position as shown in (IX). It is likely that all the arylidenearylacetonitriles are the *trans*-isomers.

Experimental

M. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford, and Mr. W. M. Eno, Bristol.

trans-2-*Methoxybenzylidenecyanoacetic* (trans-α-*Cyano*-2-*methoxycinnamic*) *Acid* (V; R = H).—2-Hydroxybenzylidenecyanoacetic acid (7·5 g.; Haarmann and Reimer, D.R.-P., 189,252), suspended in 50% ethanol (40 c.c.), was shaken during portionwise addition of 40% aqueous potassium hydroxide (75 c.c.) and methyl sulphate (50 c.c.) at 40—50° (it is essential to keep the mixture very strongly alkaline, for otherwise the product is coumarin-3-carboxylic acid). The now pale yellow solution was diluted, acidified, and boiled to convert unchanged 2-hydroxybenzylidenecyanoacetic acid into coumarin-3-carboxylic acid, and the solid crystallised twice from ethanol, giving *trans*-2-methoxybenzylidenecyanoacetic acid (5·0 g.) as yellow prisms, m. p. 211—212°, identical (mixed m. p.) with that prepared by condensation of *o*-methoxybenzaldehyde with sodium cyanoacetate (McRae and Hopkins, *Canad. J. Res.*, 1932, **7**, *B*, 248). The crystalline acid shows a blue fluorescence in ultra-violet light, but solutions of the acid do not fluoresce.

Esterification (Fischer–Speier) gave the ethyl ester as greenish-yellow prisms, m. p. 76—77° (Dave and Nargund, *loc. cit.*); this *trans*-ester (mixed m. p.) was also obtained from *o*-methoxybenzaldehyde (20 g.), ethyl cyanoacetate (17 g.), and piperidine (0·5 c.c.) in ethanol (100 c.c.) by boiling for 1 minute and cooling (yield, 29·4 g.).

2-Hydroxybenzylidenemalononitrile (VI; R = H).—To a solution of salicylaldehyde (5 g.) and malononitrile (2·6 g.) in ethanol (20 c.c.) was added piperidine (2 drops), heat being evolved. A very pale yellow solid separated from the cooled orange-red solution; after being washed with cold alcohol this product (5·5 g.) had m. p. 167° (decomp.) (Found: C, 69·5; H, 3·4; N, 16·0. $C_{10}H_6ON_2$ requires C, 70·6; H, 3·5; N, 16·4%). This *2-hydroxybenzylidenemalononitrile* must be handled with care (see p. 120). Like *trans*-2-hydroxybenzylidenecyanoacetic acid (I; R = H) it could not be recrystallised unchanged. It differs from the reddish-yellow substance, m. p. 183—184°, prepared in a similar way by Hinrichsen and Lohse (*Annalen*, 1904, **336**, 344), and claimed, without analytical support, to be the dinitrile (VI; R = H).

3-Cyanocoumarin (III; R = H).—2-Hydroxybenzylidenemalononitrile (5 g.) was dissolved, by shaking, in 4N-hydrochloric acid (300 c.c.), and after a few minutes 3-cyanocoumarin began to separate; the reaction is faster at 60°. The washed product (4·6 g., 92%) had m. p. 184—185° before and after crystallisation from ethanol, from which it separated in almost colourless prisms (Found: N, 8·3. Calc. for $C_{10}H_5ON$: N, 8·2%). 3-Cyanocoumarin, m. p. 182°, was prepared by Bechert (*J. pr. Chem.*, 1894, **50**, 23) from salicylidenebismalonic ester and by Sastry and Seshadri (*Proc. Indian Acad. Sci.*, 1942, **16**, *A*, 29) from salicylaldehyde, ethyl cyanoacetate, and piperidine (30% yield).

cis-*2-Methoxybenzylidenecyanoacetic Acid* (VII; R = H).—The conditions necessary to obtain this compound are critical. 3-Cyanocoumarin (3·8 g.) was shaken for 10 minutes with N-sodium hydroxide (120 c.c.) at 30°; most of the solid dissolved to a yellow solution, and then methyl sulphate (4 × 2 c.c.) was added during 45 minutes with continual shaking at 25—30°. After a further ¼ hour, the solution was cooled, acidified with dilute hydrochloric acid, and kept at 0° for 1 hour, and the pale yellow solid was washed and then shaken with dilute aqueous sodium hydrogen carbonate (100 c.c.). Insoluble 3-cyanocoumarin (2·7 g.) was collected, and the chilled filtrate acidified, giving a yellow solid (1·15 g., m. p. 156°). This was crystallised from a solution saturated at 30° in a mixture of methylene chloride and light petroleum (b. p. 60—80°) by slowly cooling to −5°, giving cis-*2-methoxybenzylidenecyanoacetic* (cis-α-*cyano*-2-*methoxycinnamic*) *acid* as bright yellow needles, m. p. 159—160° [Found: C, 65·0; H, 4·5; N, 6·6; OMe, 15·0. $C_{10}H_6O_2N(OMe)$ requires C, 65·1; H, 4·4; N, 6·9; OMe, 15·2%]. After melting at 159—160° it resolidifies at 160° in 30 seconds, and then has m. p. 208° owing to conversion into the *trans*-acid (V; R = H). More vigorous methylation leads to a mixture of *cis*- and *trans*-methylated acids.

Solutions of this acid are not fluorescent. In ultra-violet light the crystals at first appear brown, but in about 5 minutes develop a yellow-green fluorescence. This may be due to change in crystalline form, since solution in, *e.g.*, acetone and evaporation of the solvent gives again the non-fluorescent material with which the changes may be repeated.

Dimerisation of Ethyl trans-*2-Methoxybenzylidenecyanoacetate*.—This ester (2·7 g.; m. p. 76—77°) was finely powdered, enclosed in a slowly rotating (20—30 r.p.m.), clear, silica tube (15 × 3 cm.), and irradiated with ultra-violet light for 9 days; the m. p.s after 1, 5, and 9 days were 75—115°, 84—135°, and 110—140° respectively. The product was spread in a thin, compact layer on porous porcelain and kept at 80—85° for 12 hours, leaving a residue (m. p. 146—152°) which, twice crystallised from ethanol, gave the *dimeride* as a colourless microcrystalline powder (1·51 g.), m. p. 163° (Found: C, 67·5; H, 5·7; N, 6·3%; *M*, ebullioscopic in benzene, 469. $C_{26}H_{24}O_6N_2$ requires C, 67·5; H, 5·6; N, 6·1%; *M*, 462). Unchanged starting material was obtained from the porcelain.

trans-*5-Bromo-2-hydroxybenzylidenecyanoacetic* (trans-*5-Bromo-α-cyano-2-hydroxycinnamic*) *Acid* (I; R = Br).—5-Bromo-2-hydroxybenzaldehyde (4 g.; Auwers and Burger, *Ber.*, 1904, **37**, 3934) was condensed with alkaline, aqueous sodium cyanoacetate according to Lapworth and McRae (*J.*, 1922, **121**, 1700), giving, after washing with water and benzene, the *acid* as a bright yellow powder (4·9 g.), m. p. 167—168° (decomp.) (Found: N, 5·1; Br, 29·9. $C_{10}H_6O_3NBr$ requires N, 5·2; Br, 31·0%). Like other *trans-o*-hydroxybenzylidenecyanoacetic acids, this acid cannot be recrystallised unchanged, and its colour fades and the m. p. rises on several weeks' storage.

6-Bromocoumarin-3-carboxylic Acid (II; R = Br).—The acid (I; R = Br) (325 mg.) was boiled with water (30 c.c.) for a few minutes, and the colourless solution acidified and cooled. The precipitated 6-bromocoumarin-3-carboxylic acid (II; R = Br) (300 mg.) crystallised from

dilute ethanol in needles, m. p. 198° (Found : C, 45·0; H, 1·9; Br, 29·5. Calc. for $C_{10}H_5O_4Br$: C, 44·6; H, 1·9; Br, 29·7%) (Pandya and Pandya, *Proc. Indian Acad. Sci.*, **1943**, **18**, *A*, **164**, prepared this acid from 5-bromo-2-hydroxybenzaldehyde and malonic acid, and record m. p. 200°).

trans-5-*Bromo*-2-*methoxybenzylidenecyanoacetic Acid* (V; R = Br).—(*a*) Methylation of the phenolic acid (I; R = Br) (4·9 g.) essentially as described in the case of the acid (I; R = H) gave a mixture of (V; R = Br) and 6-bromocoumarin-3-carboxylic acid (II; R = Br). These were separated by 3% aqueous sodium hydrogen carbonate (400 c.c.) in which the latter is very sparingly soluble, filtering, and acidifying the solution slowly; the colourless acid (II; R = Br), first precipitated, is removed, and is followed by the yellow acid (V; R = Br) (1·1 g.). The trans-5-*bromo*-2-*methoxybenzylidenecyanoacetic* (trans-5-*bromo*-α-*cyano*-2-*methoxycinnamic*) *acid* separated from ethanol in prisms, m. p. 240—241° (Found : C, 47·5; H, 2·9; N, 4·8; Br, 28·9. $C_{11}H_8O_3NBr$ requires C, 46·8; H, 2·8; N, 5·0; Br, 28·4%). It shows a pale green fluorescence in ultra-violet light.

(*b*) 5-Bromo-2-methoxybenzaldehyde (Shapiro and Smith, *J.*, **1946**, **143**) (3 g.) was condensed with warm, alkaline sodium cyanoacetate [see preparation of acid (I; R = Br)], giving the acid (V; R = Br) (2·8 g.), which after crystallisation from ethanol had m. p. and mixed m. p. 241—242°.

6-*Bromo*-3-*cyanocoumarin* (III; R = Br).—5-Bromo-2-hydroxybenzaldehyde (5 g.) was condensed with malononitrile (1·8 g.) as in the case of salicylaldehyde (above), giving crude 5-bromo-2-hydroxybenzylidenemalononitrile (5·1 g.), m. p. 174—175° (decomp.) (Found : N, 13·0. $C_{10}H_5ON_2Br$ requires N, 11·3%), which could not be crystallised unchanged. This substance is a powerful sternutator and irritant. The dinitrile (4 g.) was converted by dilute hydrochloric acid, as in the case of compound (VI; R = H), into 6-*bromo*-3-*cyanocoumarin* (3·5 g.), which crystallised from ethanol (charcoal) in almost colourless prisms, m. p. 200—201° (Found : C, 47·7; H, 1·6; N, 5·4; Br, 33·0. $C_{10}H_4O_2NBr$ requires C, 48·0; H, 1·6; N, 5·6; Br, 32·0%). This cyanocoumarin is precipitated unchanged from a solution in N-sodium hydroxide at 30°, but if the alkaline solution is boiled for 5 minutes acidification gives *trans*-5-bromo-2-hydroxybenzylidenecyanoacetic acid (I; R = Br).

cis-5-*Bromo*-2-*methoxybenzylidenecyanoacetic Acid* (VII; R = Br).—6-Bromo-3-cyanocoumarin (2·25 g.) was methylated in alkaline solution as in the preparation of *cis*-2-methoxybenzylidenecyanoacetic acid (VII; R = H). From the mixed product was isolated unchanged 6-bromo-3-cyanocoumarin (1·4 g.), insoluble in aqueous sodium hydrogen carbonate, and the filtrate yielded a solid (0·85 g.) which was crystallised twice from benzene, giving cis-5-*bromo*-2-*methoxybenzylidenecyanoacetic* (cis-5-*bromo*-α-*cyano*-2-*methoxycinnamic*) *acid* as aggregates of pale yellow, microscopic prisms (Found : C, 47·1; H, 3·0; N, 4·8; Br, 28·7. $C_{11}H_8O_3NBr$ requires C, 46·8; H, 2·8; N, 5·0; Br, 28·4%), m. p. (very rapid heating) 165° followed by immediate resolidification and final melting at 237—239° owing to conversion into the *trans*-acid (V; R = Br). The solid acid shows the same phenomena in ultra-violet light as does *cis*-2-methoxybenzylidenecyanoacetic acid (VII; R = H).

Ethyl trans-5-*Bromo*-2-*methoxybenzylidenecyanoacetate*.—(*a*) 5-Bromo-2-methoxybenzaldeyde (2·5 g.), ethyl cyanoacetate (1·5 g.), ethanol (10 c.c.), and piperidine (2 drops) were warmed and cooled, giving *ethyl* trans-5-*bromo*-2-*methoxybenzylidenecyanoacetate* (3·2 g.) as pale yellow crystals, m. p. 103° (Found : C, 50·6; H, 3·9; N, 4·2; Br, 26·2. $C_{13}H_{12}O_3NBr$ requires C, 50·4; H, 3·9; N, 4·5; Br, 25·8%), from ethanol. (*b*) Esterification (Fischer–Speier) of *trans*-5-bromo-2-methoxybenzylidenecyanoacetic acid (V; R = Br) gave the same ester in 86% yield. This substance is not dimerised when exposed to ultra-violet light.

trans-2 : 4-*Dimethoxybenzylidenecyanoacetic* (trans-α-*Cyano*-2 : 4-*dimethoxycinnamic*) *Acid*.—(*a*) 2 : 4-Dimethoxybenzaldehyde (5 g.), with alkaline, aqueous sodium cyanoacetate as in the previous cases, gave the *acid* (88%) as yellow needles, m. p. 255° (decomp.) (Found : C, 61·8; H, 4·9; N, 5·9. $C_{12}H_{11}O_4N$ requires C, 61·8; H, 4·7; N, 6·0%), from ethanol. It gives a yellow fluorescence in ultra-violet light. (*b*) 2-Hydroxy-4-methoxybenzylidenecyanoacetic acid was treated with methyl sulphate and alkali, and the product crystallised several times from dioxan and finally from ethanol, giving *trans*-2 : 4-dimethoxybenzylidenecyanoacetic acid (*ca.* 20%) identical with that obtained above.

3-*Cyano*-7-*methoxycoumarin*.—2-Hydroxy-4-methoxybenzaldehyde (8 g.) and malononitrile (3·4 g.) gave, as in the cases of the dinitriles (VI; R = H and Br), crude 2-hydroxy-4-methoxybenzylidenemalononitrile (10·3 g.), m. p. 162—165° (decomp.), which could not be crystallised unchanged (Found : N, 15·3. Calc. for $C_{11}H_8O_2N_2$: N, 14·0%). This dinitrile with dilute hydrochloric acid [see preparations of the cyanocoumarins (III; R = H and Br)] yielded

3-*cyano*-7-*methoxycoumarin* (80%), needles, m. p. 221—222° (Found: C, 65·4; H, 3·7; N, 6·7. $C_{11}H_7O_3N$ requires C, 65·7; H, 3·5; N, 7·0%), from ethanol. Dilute solutions of this compound show strong blue-violet fluorescence. Methylation to *cis*-2 : 4-dimethoxybenzylidenecyanoacetic acid could not be achieved.

Ultra-violet absorption spectra characteristics of cis- *and* trans-R·CH:C(CN)·CO_2H *in* EtOH.

R	$\lambda_{max.}$, mμ (log ε)	$\lambda_{min.}$, mμ (log ε)
cis-o-Methoxyphenyl	225(4·02) 279(4·05) 323(3·94)	222(4·01) 247(3·65) 304(3·86)
trans- ,, ...	229(3·95) 284(4·04) 334(3·96)	222(3·92) 249(3·55) 311(3·85)
cis-5-Bromo-2-methoxyphenyl ...	224(4·18) 281(4·03) 341(3·80)	— 258(3·84) 316(3·70)
trans- ,, ,, ...	224(4·18) 282(4·06) 345(3·82)	— 258(3·82) 320(3·70)

Ethyl trans-2 : 5-*Dimethoxybenzylidenecyanoacetate*.—Esterification of *trans*-2 : 4-dimethoxybenzylidenecyanoacetic acid (Fischer–Speier) gave the ethyl ester (80%), pale yellow needles (from ethanol), m. p. 142—143°, identical (mixed m. p.) with that prepared from 2 : 4-dimethoxybenzaldehyde and ethyl cyanoacetate (Kauffmann, *Ber.*, 1919, **52**, 1433). It is not dimerised by ultra-violet light.

THE UNIVERSITY, BRISTOL. [*Received, September 20th*, 1952.]

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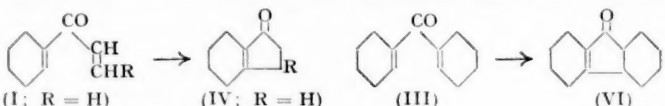
23. *Preparation of* cyclo*Pentenones from the Products of Interaction of Acid Chlorides and Olefins.*

By G. BADDELEY, H. T. TAYLOR, and (in part) W. PICKLES.

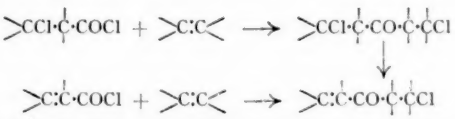
Ethylene readily combines with acid chloride–aluminium chloride complexes in solution in ethylene chloride or methylene chloride to provide 2-chloroethyl ketones and their products of dehydrochlorination. The products of interaction of *cyclo*hexene and the chlorides of β-chloropropionic, crotonic, and *cyclo*hex-1-enecarboxylic acid severally afford *cyclo*pentenones by the action of phosphoric acid in solution in formic acid (98%).

RECENTLY, Braude and Coles (*J.*, 1952, 1430) have shown that the three divinyl ketones (I, II, and III), which they prepared by direct alkenylation with lithium alkenyls (*J.*, 1950, 2012, 2014), afford the *cyclo*pentenone derivatives (IV, V, and VI) by the action of phosphoric acid in formic acid. Interaction of olefins and acid chlorides and anhydrides



(I; R = H) (II; R = Me) (IV; R = H) (V; R = Me) (III) (VI)

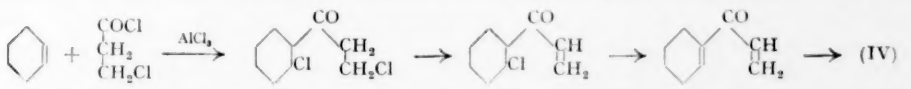
through the agency of aluminium chloride affords ready access to ββ′-dichloro-ketones and the corresponding vinyl ketones resulting from monodehydrochlorination; the reaction can be formulated:



We now report that these products, though prevented by the incursion of polymerisation from being a convenient source of divinyl ketones, can provide *cyclo*pentenones by the action of phosphoric acid in formic acid; (IV, V, and VI) have been prepared in this way. The preparation of (IV) is formulated below; (V) and (VI) were similarly obtained from the products of interaction of *cyclo*hexene and the chlorides of crotonic and *cyclo*hex-1-enecarboxylic acid respectively.

To obtain optimum yields of halogenated ketones on interaction of acid halides and olefins in the presence of aluminium chloride, Catch, Elliot, Hey, and Jones (*J.*, 1948, 278) used no solvent other than the acyl halide itself. Since vigorous agitation was essential, excess of the acyl halide was used in reactions in which, when molar quantities of the

reagents were used, stirring was difficult; poorer yields were obtained by earlier investigators employing inert diluents such as petroleum or carbon disulphide. These diluents are poor solvents for the polar complexes obtained by combination of acid and aluminium chlorides and since methylene and ethylene chlorides have proved to be valuable solvents



for the conventional Friedel–Crafts ketone synthesis in the aromatic series, we have employed them in the aliphatic series. With ethylene, the best yields were obtained in the absence of hydrogen chloride and in the presence of a small excess of aluminium chloride and are given in the Table. The theoretical volume of ethylene was readily absorbed in each instance but simultaneous formation of vinyl ketones, which became more important with rise in temperature (Wieland and Beltog, *Ber.*, 1922, **55**, 2246) and on storage of the reaction mixture, prevented quantitative production of 2-chloroethyl ketones. Similarly, interaction of *cyclo*hexene and the chlorides of β-chloropropionic, crotonic, and *cyclo*hex-1-enecarboxylic acid severally afforded mixtures which contained less chlorine than is required for the products of addition. These mixtures are not readily dehydrochlorinated and unlike 2-chloro*cyclo*hexyl methyl ketone (Christ and Fuson, *J. Amer. Chem. Soc.*, 1937, **59**, 893) contain chlorine after distillation from anhydrous sodium carbonate. The results are summarised in the Table. Both before and after distillation from sodium carbonate, these mixtures evolve hydrogen chloride by the action of phosphoric acid in formic acid (98%) at 90° and afford *cyclo*pentenone derivatives. We are indebted to Dr. E. A. Braude for providing samples of the dinitrophenylhydrazones of the *cyclo*pentenones (IV and V).

Interaction of ethylene and R·COCl–$AlCl_3$ *in methylene and ethylene chlorides at* −5°.

R·COCl	Product	Yield (%)	B. p./mm.	Chlorine (%) Found	Reqd.
CH_3·COCl	CH_3·CO·CH_2·CH_2Cl	40 (40)	46°/14	33·1	33·3
CH_2Cl·COCl	CH_2Cl·CO·CH_2·CH_2Cl	83 (45)	68°/0·2	50·0	50·3
CH_3·CHCl·COCl	CH_3·CHCl·CO·CH_2·CH_2Cl	78 (60)	62°/1	46·2	45·8
CH_2Cl·CH_2·COCl	CH_2·Cl·CH_2·CO_2·CH_2·CH_2Cl	53 (30)	78°/0·8	46·1	45·8

Interaction of cyclo*hexene and* R·COCl–$AlCl_3$ *in methylene and ethylene chlorides at* −5°.

R·COCl	Cl (%) before distn.	Cl (%) theor.	Cl (%) after distn.
CH_3·COCl	21·8	22·1	**0**
C_6H_5·COCl	12·0	15·8	Not distilled
CH_3·CH:CH·COCl	10·6	19·1	8·4
CH_2Cl·CH_2·COCl	29·0	34·0 (dichloride) 20·6 (monochloride)	13·4

Since aryl vinyl ketones and aryl 2-chloroethyl ketones readily afford indanones by the action of aluminium chloride–hydrogen chloride, we have attempted, though without success, to apply this reagent to the preparation of the above *cyclo*pentenones.

Experimental

1 : 2 : 3 : 4 : 5 : 6 : 7 : 8 : 10 : 11-*Decahydrofluorenone*.—1-Anilino*cyclo*hexanecarboxylic acid (40 g.), obtained from *cyclo*hexanone as described by Walther and Hubner (*J. pr. Chem.*, 1916, **93**, 124) and Betts, Muspratt, and Plant (*J.*, 1927, 1312), provided a mixture of aniline and *cyclo*hex-1-enecarboxylic acid when melted and then strongly heated under reduced pressure. The mixture was shaken with dilute hydrochloric acid and methylene chloride, and the lower layer was extracted with sodium carbonate solution; on acidification, the alkaline extracts afforded a colourless oil which was extracted with methylene chloride, dried (Na_2SO_4), and distilled; *cyclo*hex-1-enecarboxylic acid (8 g.), b. p. 246—248°, m. p. 33°, was obtained and this afforded the corresponding acid chloride (9 g.), b. p. 202—204° (Kenner and Wain, *Ber.*, 1939, **72**, 456) by the action of thionyl chloride. The acid chloride (9 g.) was added to a suspension of finely powdered aluminium chloride (15 g. > 1 mol.) in methylene chloride (50 ml.), and the liquid phase was decanted from undissolved aluminium chloride and filtered through a plug of

glass wool into a reaction vessel from which atmospheric moisture was excluded. The solution was vigorously stirred, at −10°, and *cyclo*hexene (6 g., 1·2 mols.) was added during 25 minutes, and the mixture, the temperature of which was not allowed to exceed −5°, was stirred for a further 10 minutes and then poured into dilute hydrochloric acid and ice. The organic layer was dried (K_2CO_3), and methylene chloride was removed at 0° under reduced pressure; the residue was a pale brown viscous oil (10 g.) (Found: Cl, 12·0. Calc. for $C_{13}H_{17}OCl$: Cl, 15·8%). This product (5 g.) was heated with phosphoric acid (4 g.) and formic acid (98%; 8 g.) at 90° for 18 hours under nitrogen; hydrogen chloride was evolved and the product was poured into water and extracted with ether (2 × 30 ml.); the extract was dried (K_2CO_3) and distilled. The required decahydrofluorenone (2·5 g.), b. p. 126—127°/0·1 mm., and m. p. 20° [m. p. 25° after crystallisation from light petroleum (b. p. 0—40°)], formed an oxime, m. p. 133—134°; Braude and Coles (*loc. cit.*) record m. p.s 26° and 133—134° respectively.

4 : 5 : 6 : 7-*Tetrahydro*-3-*methylindanone*.—Crotonyl chloride (10·4 g.) was added to a suspension of aluminium chloride (20 g.) in methylene chloride; the solution was decanted from undissolved aluminium chloride, then cooled to −10°, and *cyclo*hexene (8·2 g.) was gradually added. Working up as in the previous case gave a dark material (14 g.) (Found: Cl, 10·6. Calc. for $C_{10}H_{15}OCl$: Cl, 19·0%) which was distilled from anhydrous sodium carbonate (2—3 g.) and provided a mixture (8 g.), b. p. 80—110°/0·25 mm. (Found: Cl, 8·4%). [In another experiment this mixture was fractionally distilled, providing a fraction (1 g.), b. p. 65—68°/0·25 mm., which was probably *cyclo*hex-1-enyl propenyl ketone, b. p. 64—65°/0·3 mm. (Braude and Coles, *J.*, 1952, 1430), and a residue which polymerised.] The mixture (7 g.) was heated with phosphoric acid (3 g.) and formic acid (98%; 8 g.) at 80—90° for 4 hours under nitrogen; hydrogen chloride was evolved. The product, worked up as described above, gave the indanone (4 g.), b. p. 130°/16 mm. It formed a semicarbazone which separated from aqueous methanol in prisms, m. p. 219° (decomp.) [Braude and Coles, *loc. cit.*, give m. p. 214—217° (decomp.)], and a 2 : 4-dinitrophenylhydrazone, m. p. 246°; the m. p. was not depressed on admixture of the sample with the 2 : 4-dinitrophenylhydrazone described by Braude and Coles, *loc. cit.*, who give m. p. 246—248°.

4 : 5 : 6 : 7-*Tetrahydroindanone*.—β-Chloropropionyl chloride (12·7 g.) was gradually added to a suspension of powdered aluminium chloride (20 g.) in methylene chloride (100 ml.). The solution was decanted from undissolved aluminium chloride and cooled to −10°; *cyclo*hexene (8·2 g.) was added at such a rate (during 30 min.) that the temperature of the reaction mixture did not exceed −5°. The product was worked up as above and provided a residue (13 g.) (Found: Cl, 29·0. Calc. for $C_9H_{14}OCl_2$: Cl, 34·0%) after evaporation of methylene chloride. Distillation from anhydrous sodium carbonate afforded a fraction (7 g.), b. p. 105—115°/15 mm. (Found: Cl, 13·4. Calc. for $C_9H_{13}OCl$: Cl, 20·6%). (Fractional distillation of this product in another experiment effected polymerisation.) The product (5 g.), together with phosphoric acid (2 g.) and formic acid (98%; 6 g.), was kept at 90° for 3 hours under nitrogen. Hydrogen chloride was evolved and the product was worked up as above. The required indanone (4 g.), b. p. 126—128°/15 mm. (Braude and Coles, *loc. cit.*, give b. p. 126—128°/14 mm.), formed a dinitrophenylhydrazone which crystallised from benzene in orange plates, m. p. 243—244°, and did not, by admixture, depress the m. p. of the 2 : 4-dinitrophenylhydrazone described by Braude and Coles, *loc. cit.*, who give m. p. 235—238°. In a further experiment, the product (17 g.) of the Friedel–Crafts reaction was allowed to react with phosphoric acid (8 g.) in formic acid (98%; 16 g.) and afforded the required indanone (4·5 g.).

Interaction of Acid Chlorides and Ethylene in Methylene or Ethylene Chloride as Solvent.—The acid chloride (0·25 mole) was added to a suspension of finely powdered aluminium chloride (0·30 mole) in solvent (150 ml.). The solution was decanted from undissolved aluminium chloride, and poured through a plug of glass wool into the reaction vessel which was cooled in a freezing mixture. Dry ethylene was passed into the agitated solution at −10°; absorption was rapid and ceased when ethylene (5·5 l.) has been absorbed. The temperature of the reaction mixture was not allowed to exceed −5°. The product was then poured into dilute hydrochloric acid and ice, and the organic layer was dried (Na_2SO_4) and distilled under reduced pressure. The best yields (see Table) of the 2-chloroethyl ketones were usually obtained (*a*) when the reaction mixtures were not freed from undissolved aluminium chloride and (*b*) when the reaction mixtures were freed from hydrogen chloride by a stream of dry nitrogen before ethylene was introduced. The yields given in parentheses in the Table were obtained by Catch, Elliot, Hey, and Jones (*loc. cit.*).

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24. *Acyl Migration during Dephosphorylation and a Suggested Mechanism.*

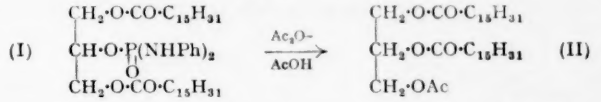
By T. H. Bevan, D. A. Brown, G. I. Gregory, and T. Malkin.

Derivatives of 1 : 3-dipalmitoylphosphatidic acid yield 1-acetyl-2 : 3-dipalmitin when heated with acetic acid–acetic anhydride. For this rearrangement, a Walden inversion mechanism is suggested, in support of which it is found that active 1-methylheptyl diphenyl phosphate undergoes inversion when converted into 1-methylheptyl acetate under the above conditions.

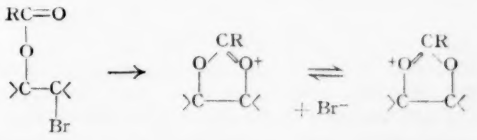
During synthetic work on phosphatides, we had occasion to remove protecting anilido-groups from the dianilide (I) of 1 : 3-dipalmitoylphosphatidic acid. Having found that the method suggested by Zetszche and Buttiker (*Ber.*, 1940, **73**, 47), involving use of acetic acid, was ineffective, we employed more drastic conditions: the dianilido-compound was refluxed with acetic anhydride–acetic acid (1 : 4 by vol.) for several hours, but the phosphate group was entirely removed. The resulting product was an acetyl dipalmitin, which we first assumed to be 2-acetyl-1 : 3-dipalmitin.

In the hope that this reaction might be of value in determining the position of phosphate groups, we submitted the following related compounds to the same treatment: 2′-aminoethyl 1 : 2- and 1 : 3-dipalmitoylphosphatidoate (α- and β-kephalin), 1 : 2-dipalmitoylphosphatidylcholine (α-lecithin), 1 : 2-dipalmitoylphosphatidic acid, and diphenyl 1 : 2-dipalmitoylphosphatidoate. To our surprise, we obtained in all cases the same acetyl dipalmitin as in our original experiment, in practically quantitative yields.

By synthesis of the two acetyl dipalmitins, and *X*-ray and melting-point comparisons, our product was found to be 3-acetyl-1 : 2-dipalmitin. Thus, in two of the above cases, acyl migration takes place during dephosphorylation [see (I) ⟶ (II)].

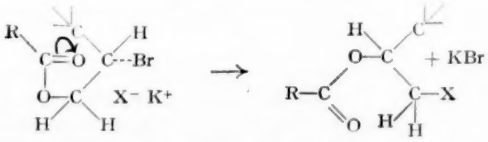


Fairbourne and Cowdrey (*J.*, 1929, 129) observed a number of similar migrations, but came to no decision concerning the identity of the final product; *e.g.*, the palmitates of 1 : 2- and 1 : 3-dibromohydrins and silver *p*-nitrobenzoate yielded the same di-*p*-nitrobenzoyl-monopalmitin. Winstein and Buckles (*J. Amer. Chem. Soc.*, 1942, **64**, 2780, 2787) postulated the formation of an intermediate resonant ion for certain similar reactions, *viz.*:



but this implies the possibility of acyl migration from $C_{(1)}$ to $C_{(2)}$ or from $C_{(2)}$ to $C_{(1)}$, whereas only the former occurs in our experiments. This also holds for the quoted dibromohydrin experiment, where we have identified Fairbourne and Cowdrey's final product as 1 : 3-di-*p*-nitrobenzoyl-monopalmitin. It is probable that the course of these reactions is determined by steric influences. When, *e.g.*, the halogen is on $C_{(2)}$, the opposite face of this atom is shielded by the groups on $C_{(1)}$ and $C_{(3)}$ and a normal Walden inversion is prevented. Moreover, as is seen from the following scheme, an acyl group on $C_{(1)}$ or $C_{(3)}$ is favourably placed for combination with $C_{(2)}$. A more obvious example of this shielding effect is the Wagner–Meerwein transformation, for which Bartlett and Pockel (*ibid.*, 1937, **59**, 820) have suggested a Walden mechanism, and there is little doubt that this effect is important in many similar migrations.

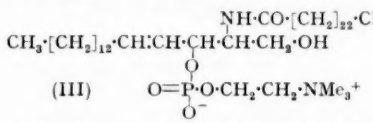
A further interesting point arises out of our dephosphorylation experiments. As we have definitely established that migration occurs, we can infer, by reversing our previous argument, that the C–O bond of the phosphate ester is broken, *i.e.*, the removal of the



phosphate group should be accompanied by a Walden inversion. This was suggested by Robinson (*Nature*, **1927**, **120**, 44) as a mode of biochemical conversion of glucose-4 phosphate into galactose; but, apparently, no case of inversion during enzymic dephosphorylation is known (Raymond in Gilman's "Organic Chemistry," John Wiley and Sons, New York, **1943**, p. 1608); nor were Percival and Percival (*J.*, **1945**, 874) able to find evidence for inversion during the alkaline hydrolysis of certain sugar phosphates.

On the other hand, Blumenthal and Herbert (*Trans. Faraday Soc.*, **1945**, **41**, 611) have shown by the hydrolysis of trimethyl phosphate with water containing ^{18}O that, whilst alkaline hydrolysis cleaves the O–P bond (*i.e.*, there is no inversion), neutral and acid hydrolysis cleaves the O–C bond. In spite, therefore, of the prevalent view that there is no inversion during dephosphorylation, there seemed to be good reason to suppose that inversion should take place during acid hydrolysis, and, on dephosphorylating the diphenyl phosphate of (+)-octan-2-ol, we obtained the (−)-acetate, although, from the rotation value, some racemisation had also occurred.

In order to test the generality of our dephosphorylation method, we extended it to octadecyl phosphate and to sphingomyelin (III); the former was converted quantitatively



(III)

into octadecyl acetate, and the latter yielded a product which gave correct analyses for *OO*-diacetyl-*N*-lignocerylsphingosine and had a melting point very close to that of the compound obtained from sphingomyelin by Thannhauser and Reichel (*J. Biol. Chem.*, **1940**, **135**, 15) by enzymic dephosphorylation followed by acetylation. This change is of special interest because the position of the phosphate group (whether 1 or 3) is not known. Proof of inversion during dephosphorylation would decide in favour of position 3.

Experimental

Half-gram amounts of each of the following were separately heated under reflux with 10 c.c. of acetic anhydride–acetic acid (1 : 4 by vol.) for 8 hours; 1 : 3-dipalmitoylphosphatidic dianilide; 2′-aminoethyl 1 : 3-dipalmitoylphosphatidoate; 1 : 2-dipalmitoyl-phosphatidylcholine and -phosphatidic acid, diphenyl 1 : 2-dipalmitoylphosphatidoate. In all cases there separated on cooling, in practically quantitative amount, crystalline 3-acetyldipalmitin, which after one crystallisation from ethanol melted at 51°. Averill, Roche, and King (*J. Amer. Chem. Soc.*, 1929, **51**, 870) give 51—52°, but as the m. p. of the isomeric 2-acetyldipalmitin is 54° (Averill *et al.*) we prepared the two isomers by acylation of 1 : 2- and 1 : 3-dipalmitin, finding m. p.s of 51° and 53° respectively, and determined their short *X*-ray spacings, which were as follows: 3-Acetyldipalmitin: 5·27 moderate; 4·14 strong (very thick; possibly two unresolved lines); 3·77 strong. 2-Acetyldipalmitin: 5·18 weak; 4·54 strong; 3·76 strong. These spacings and mixed m. p.s established the identity of the dephosphorylation product as 3-acetyldipalmitin.

When the isomeric dipalmitins were heated for 8 hours with the dephosphorylating agent, they gave isomeric acetyl derivatives, and hence no migration takes place under these conditions.

Dephosphorylation of 1-Methylheptyl Diphenyl Phosphate.—(+)-Octan-2-ol (3·9 g., 0·03

mol.; $[\alpha]_D^{20}$ +9·7°) was added in small portions to a solution of diphenyl chlorophosphonate (16 g., 0·06 mol.) in pyridine (40 c.c.). After 48 hours, the solution was poured into 2N-hydrochloric acid (300 c.c.), and the oil which separated was extracted with ether. The ether was removed after successive treatments with N-hydrochloric acid, sodium hydrogen carbonate solution, and water, and final drying (Na_2SO_4). Residual pyridine was removed at 0·3 mm. There remained (+)-1-methylheptyl diphenyl phosphate (84%) as a viscous oil. This was refluxed for 36 hours with acetic anhydride (10 c.c.) and acetic acid (40 c.c.). After cooling, the solution was poured into an excess of saturated sodium hydrogen carbonate solution, and the precipitated oil extracted with ether. After washing, drying, and removal of ether, the residue was distilled, to yield 1-methylheptyl acetate (2·9 g.), b. p. 84—85°/20 mm., $[\alpha]_D^{20}$ −1·9°. Pickard and Kenyon (*J.*, 1914, 830) give $[\alpha]_D^{20}$ +6·84°.

In the above experiment, refluxing was for a longer time than usual to ensure complete dephosphorylation, and this may have brought about some racemisation. Alternatively, the replacement itself may involve some racemisation.

Dephosphorylation of Sphingomyelin.—Sphingomyelin (cf. Bevan, Gregory, Poole, and Malkin, *J.*, 1951, 841) (1 g.; m. p. 212°) was heated with the acetic anhydride—acetic acid (1 : 4 by vol.; 10 c.c.) under reflux for 8 hours. On cooling, a solid separated and this was filtered off (0·6 g.; m. p. 68—70°). Three crystallisations from methanol gave *O*-diacetyl-*N*-lignoceryl-sphingosine, m. p. 72—74° (Found: C, 75·3; H, 12·3; N, 1·7. Calc. for $C_{46}H_{87}O_5N$: C, 75·3; H, 11·9; N, 1·9%). Thannhauser and Reichel (*J. Biol. Chem.*, 1940, **135**, 15) give m. p. 70—71°.

Dephosphorylation of Octadecyl Phosphate.—The phosphate (0·5 g.) was heated for 8 hours with the acetic anhydride–acetic acid mixture (5 c.c.). On cooling, octadecyl acetate separated (almost 100%). Recrystallised from ethanol, it had m. p. and mixed m. p. 32°.

1 : 2- *and* 1 : 3-*Di*-p-*nitrobenzoyl-monopalmitins.*—α- and β-Monopalmitins were acylated with *p*-nitrobenzoyl chloride in pyridine, to yield the above isomers respectively. After crystallisation from alcohol they melted at 73° and 106° respectively [Found: N (1 : 2-derivative), 4·5; (1 : 3-derivative), 4·7. Calc. for $C_{33}H_{44}O_{10}N_2$: N, 4·5%]. Fairbourne and Cowdrey give m. p. 102°.

We are grateful to Dr. J. Kenyon, F.R.S., for a generous gift of 1-methylheptyl hydrogen phthalate, and one of us (G. I. G.) thanks the Department of Scientific and Industrial Research for a grant.

THE UNIVERSITY, BRISTOL. [*Received, June 12th*, 1952.]

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25. *The Oxidation of Ferrous Hydroxide.*

By J. E. O. MAYNE.

The composition has been examined of the air-dried material produced by addition of alkalis to ferrous sulphate solution. When the pH was low, γ-Fe_2O_3,H_2O was obtained; in more alkaline solutions α-Fe_2O_3,H_2O was formed when the oxidation was fast and a material having a composition intermediate between Fe_3O_4 and γ-Fe_2O_3 when it was slow. The results are explained in terms of the oxidation and hydrolysis of a basic sulphate.

THERE is confusion in the literature regarding the composition of the material produced by oxidation of ferrous hydroxide. The nature of the product is important, not only from the academic point of view, but also in connection with the theory of the mechanism of the inhibition of the corrosion of iron by alkaline solutions. The following investigation was carried out in order to clarify the position.

It is well known that ferrous hydroxide is a white solid, which becomes green in the presence of a trace of air; if oxidation continues, the green material becomes brown and may darken. Deiss and Schikorr (*Z. anorg. Chem.*, 1928, **172**, 32) examined the reaction and concluded that the green product was a basic ferrous ferrite, $Fe(OH)\cdot O\cdot Fe(OH)_2$. On

the other hand, Girard and Chaudron (*Compt. rend.*, 1935, **200**, 127) regarded the green material as hydrated magnetite.

Krause (*Z. anorg. Chem.*, 1928, **174**, 145) investigated the effect of pH on the composition of the fully oxidised precipitate. A constant volume of N-ferrous sulphate solution was mixed with varying quantities of N-sodium hydroxide and the precipitate was filtered off, washed, and dried in air. The total iron and ferrous iron in the precipitate were then determined. When the pH of the filtrate did not exceed 5·2, the precipitate was free from ferrous iron and it was concluded that it consisted of γ-Fe_2O_3,H_2O. As the filtrate became more alkaline the ferrous oxide content of the precipitate increased to the constant value of 10·8% at pH's above 11; it was concluded that under these conditions the material was magnetite. When precipitation was by aqueous ammonia, the ferrous iron content of the precipitate did not increase so rapidly when the pH was raised. Schikorr (*ibid.*, 1930, **191**, 322) considered that any intermediate compounds, *i.e.*, ferrous ferrites, could be oxidised to hydrated ferric oxide and suggested that α-Fe_2O_3,H_2O is formed when the oxidation proceeds directly to the ferric condition, and γ-Fe_2O_3,H_2O when it proceeds *via* an intermediate ferrous ferrite.

These views concerning the final product cannot all be true. An investigation has, therefore, been made of the composition of the green intermediate compound, and its oxidation has been carried out under conditions similar to those described by Schikorr and and by Krause. The ferrous iron content of the final product was determined by analysis, and its structure by means of *X*-rays.

Experimental

The Green Intermediate Product.—Composition. This substance was prepared by mixing 25 ml. of 0·1N-ferrous sulphate with 100 ml. of N-sodium hydroxide in a 500-ml., wide-neck, conical flask; the green precipitate was then dissolved by addition of 10 ml. of 6N-sulphuric acid, and the ferrous iron content determined by titration against 0·1N-potassium dichromate (diphenylamine as indicator). It was found that 6·3% of the iron had been oxidised before titration; the amount increased to 7·7% when the precipitate had been kept for 1 hour, but the precipitate was still green. After a week's exposure the colour had darkened and 84·6% of the iron had been oxidised.

Effect of oxygen. Schikorr (*loc. cit.*, Expt. 3) dissolved 1·2 g. of $FeSO_4,7H_2O$ in 200 ml. of water and added 1·4 ml. of a 10% solution of ammonia, the stoicheiometric quantity, and the mixture had pH 5·6. Oxygen was then passed through the solution for 30 min., and the precipitate was filtered off, washed, dried at 100°, heated for 3 hours at 230°, and tested with a magnet. This experiment has now been repeated, with the following modifications. The precipitate, after being oxidised and washed, was dried at room temperature for 2 days, sheltered from dust by filter-paper. Its structure was then determined by means of *X*-rays, in a 19-cm. powder camera with cobalt radiation and an iron filter. The photographs were compared with those obtained from magnetite (Fe_3O_4), lepidocrocite (γ-Fe_2O_3,H_2O), and goethite (α-Fe_2O_3,H_2O), and proved to be those of γ-Fe_2O_3,H_2O. The precipitate was shown to be free from ferrous iron as follows: 50 ml. of 2N-hydrochloric acid were boiled and cooled in a current of carbon dioxide, a weighed portion of the dried precipitate was added, the mixture gently boiled to effect solution, and the solution cooled with the gas still passing through, and then titrated against 0·05N-potassium dichromate (barium diphenylaminesulphonate as indicator): there was a nil result.

The experiment was then repeated, the ammonia solution being replaced by 11·5 ml. of 2·5N-sodium hydroxide, so that the alkalinity of the solution was 0·1N after completion of precipitation. The dried precipitate was found to be free from ferrous ions and had the structure of α-Fe_2O_3,H_2O.

Effect of air. A similar procedure was used, except that oxygen was not bubbled through the suspension; the precipitate was allowed to settle for an hour before being filtered off, washed, and air-dried; under such conditions oxidation commenced as soon as the precipitate was formed and continued during filtration. This procedure was used by Krause (*loc. cit.*).

Varying quantities of ammonia and sodium hydroxide were used as precipitants and the pH of the filtrate was measured by means of a glass electrode. The results obtained are shown in the Table.

pH of filtrate	Fe^{++}, % precipitate	Composition of precipitate from X-ray powder photographs: Major constituent	Minor constituent
	Precipitant: Ammonium hydroxide.		
5·0	1·9	γ-Fe_2O_3,H_2O	Fe_3O_4 or γ-Fe_2O_3
5·6	2·4	γ-Fe_2O_3,H_2O	Fe_3O_4 or γ-Fe_2O_3
9·0	4·1	Fe_3O_4 or γ-Fe_2O_3	γ-Fe_2O_3,H_2O
	Precipitant: Sodium hydroxide.		
4·2	1·8	γ-Fe_2O_3,H_2O	Fe_3O_4 or γ-Fe_2O_3
5·0	3·9	Fe_3O_4 or γ-Fe_2O_3	γ-Fe_2O_3,H_2O
6·5	6·4	Fe_3O_4 or γ-Fe_2O_3	γ-Fe_2O_3,H_2O
9·3	9·3	Fe_3O_4 or γ-Fe_2O_3	—
10·6	9·1	Fe_3O_4 or γ-Fe_2O_3	—
10·6	8·1	Fe_3O_4 or γ-Fe_2O_3	—

In the last experiment the precipitate was allowed to settle for 24 hours before being filtered off.

Discussion

Addition of excess of sodium hydroxide solution to a solution of ferrous sulphate yielded a green precipitate, which contained only 6·3% of ferric iron; so it follows that the precipitate cannot have the composition ascribed to it by previous workers. Schikorr oxidised it with a current of oxygen, but it has now been found that under these conditions either α-Fe_2O_3,H_2O or γ-Fe_2O_3,H_2O is formed according to the pH at which oxidation occurs; consequently, it is difficult to accept the view that γ-Fe_2O_3,H_2O is always formed when the oxidation proceeds *via* the green intermediate compound.

When the precipitate was allowed to oxidise slowly in air at relatively low pH values it consisted mainly of γ-Fe_2O_3,H_2O, together with a small quantity of material having the cubic structure of either Fe_3O_4 or γ-Fe_2O_3. Hagg (*Z. phys. Chem.*, 1935, *B*, **29**, 95) has shown that when Fe_3O_4 is oxidised at a low temperature to γ-Fe_2O_3, the spinel structure is retained; this process is accompanied by a continuous but slight diminution of the lattice constant, so the product of oxidation should be regarded as a phase of variable composition. The dried precipitate contained 1·8% of ferrous iron; it was concluded that it contained a small quantity of either magnetite or a material having a composition intermediate between Fe_3O_4 and γ-Fe_2O_3. It should be noted that Krause (*loc. cit.*) detected ferrous ions in material prepared in this way, but he attributed their presence to an error in his method of analysis.

As the pH of the filtrate rose, the γ-Fe_2O_3,H_2O content of the dried precipitate diminished. This change was less complete when ammonia was used as the precipitant, thus confirming Krause's observation. When the pH of the filtrate exceeded 9, the precipitate showed the cubic structure of either Fe_3O_4 or γ-Fe_2O_3; from the ferrous iron content of the product, 9·2%, it can be calculated that the precipitate corresponded to a product in which a 70—75% conversion of Fe_3O_4 into γ-Fe_2O_3 had occurred. Moreover, this value is in reasonable agreement with that (8·3%) calculated from the FeO content found by Krause. There is, however, a general indication that the figures for ferrous iron obtained in this investigation are all slightly higher than those obtained by Krause, but as he did not publish full experimental details of his method, the difference cannot be resolved.

The conclusions to be drawn from this investigation are that when ferrous hydroxide is oxidised in the pH range 4—5 γ-Fe_2O_3,H_2O is formed, irrespective of the rate of oxidation; in alkaline solutions either α-Fe_2O_3,H_2O or a material having a composition intermediate between Fe_3O_4 and γ-Fe_2O_3 is produced according as oxidation is fast or slow.

It is possible that the γ-Fe_2O_3,H_2O arises from the hydrolysis of a basic salt; Arden's work (*J.*, 1950, 882) suggests that a basic sulphate is first precipitated when sodium hydroxide is run into a solution of ferrous sulphate, in the presence of air or ferric ions. In alkaline solutions the basic compound will be hydrolysed and the resulting product, which probably contains both ferrous and ferric iron, may be oxidised to either α-Fe_2O_3,H_2O or magnetite and then to γ-Fe_2O_3 according to the rate of oxidation. Deiss and Schikorr (*loc. cit.*) have suggested that when oxidation is slow, the hydrated ferric oxide first formed may interact with the remaining ferrous hydroxide to form magnetite. This explanation

agrees with the views of Forrest, Roethelli, and Brown (*Ind. Eng. Chem.*, 1931, **23**, 650) and of Girard and Chaudron (*loc. cit.*) on the formation of magnetite, and the mechanism may well be operative.

These results have an important bearing on the theory of the inhibition of the corrosion of iron by alkaline solutions. It was shown (*J.*, 1950, 3229) that the film formed on iron by sodium hydroxide solution, in the presence of air, was mainly composed of material having the cubic structure of γ-Fe_2O_3. It is now clear that such a film could be formed by oxidation of ferrous hydroxide; this possibility will be discussed in a later paper.

This investigation formed part of a programme of research carried out for the British Iron and Steel Research Association by the group of investigators associated with Dr. U. R. Evans. The author is indebted to that Association and to Dr. U. R. Evans for their support and interest, without which the work could not have been performed. He also thanks Mr. D. E. Davies for taking and interpreting the *X*-ray photographs, Dr. F. A. Bannister for the supply of a sample of lepidocrocite, and Drs. J. N. Agar and F. Wormwell for helpful criticism.

Department of Metallurgy, University of Cambridge. [*Received, July 23rd*, 1952.]

26. *Methyl-substituted αβ-Unsaturated Acids. Part I.*

By P. C. Jocelyn and N. Polgar.

In connection with investigations on the αβ-unsaturated acids of human tubercle bacilli the influence of an αβ-double bond on the rotation of optically active methyl-substituted acids has been studied by syntheses of model compounds from (+)-3 : 7-dimethyloctan-1-ol (dihydrocitronellol). Dehydrobromination of the α-bromo-substituted methyl ester derived from (−)-2 : 4 : 8-trimethylnonanoic acid * (VI) by means of alcoholic potassium hydroxide results in racemization of the product in respect of the asymmetric centre at C_γ, but pyridine dehydrobromination yields the optically active αβ-unsaturated ester (X; R = Me). Alkaline hydrolysis of the latter affords (−)-2 : 4 : 8-trimethylnon-2-enoic acid (X; R = H) which, although having the asymmetric centre adjacent to the αβ-double bond, exhibits a remarkable optical stability. This acid has a greatly increased rotation relative to the corresponding saturated acid, whereas there is no such increase if the asymmetric centre is removed further from the carboxyl group as exemplified by (−)-2 : 5 : 9-trimethyldec-2-enoic acid (XI; R = H). The relation of these findings to the structural features of the tubercle-bacilli acids is discussed.

Recent investigations in this laboratory have shown that the optically active acids of human tubercle bacilli are mixtures of saturated and unsaturated acids. The dextrorotatory fraction was found to contain αβ-unsaturated acids (Polgar, *Biochem. J.*, 1948, **42**, 206; Chanley and Polgar, *Nature*, 1950, **166**, 693) and it was noted that the rotation of these acids is greatly decreased on hydrogenation. This suggested the presence of an asymmetric centre near to the αβ-double bond and the object of the work now described has been to study optically active αβ-unsaturated acids with an asymmetric centre in the γ- and the δ-position, respectively. The work was undertaken concurrently with degradative studies which have already been reported in a preliminary note (Polgar and Robinson, *Chem. and Ind.*, 1951, 685).

The starting material chosen for the syntheses of the required optically active acids was (+)-3 : 7-dimethyloctan-1-ol (I), obtained by catalytic hydrogenation of (+)-citronellol. The main object was to prepare active 4 : 8-dimethylnonanoic * (III), 2 : 4 : 8-trimethylnonanoic (VI), and 2 : 5 : 9-trimethyldecanoic acid (IX), and to convert them into the corresponding αβ-unsaturated acids by α-bromination and subsequent dehydrobromination.

* Geneva nomenclature (CO_2H = 1) is used throughout.

(−)-4 : 8-Dimethylnonanoic acid (III), $[\alpha]_D$ −1·0°, was obtained by converting (I) into the bromide (II) and carboxylating the derived Grignard complex.

(I) $CH_3{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}OH$ $CH_3{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CHMe{\cdot}CH_2{\cdot}CO_2H$ (IV)

(II) $CH_3{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}Br$ $CH_3{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CHMe{\cdot}CH_2Br$ (V)

(III) $CH_3{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}CO_2H$ $CH_3{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CHMe{\cdot}CH_2{\cdot}CHMe{\cdot}CO_2H$ (VI)

For the preparation of (−)-2 : 4 : 8-trimethylnonanoic acid (VI) the intermediate was (+)-3 : 7-dimethyloctanoic acid (IV). The latter, obtained previously by way of citronellic acid (Semmler, *Ber.*, 1893, **26**, 2254; Paal, *Chem. Zentr.*, 1917, II, 145) or *via* dihydrocitronellal (Sabetay and Bléger, *Bull. Soc. chim.*, 1928, **43**, 843; von Braun and Kaiser, *Ber.*, 1923, **56**, 2268), was more conveniently made from (I) by oxidation with chromic acid in acetone (cf. oxidation of 5-methyldecan-1-ol, Leese and Raphael, *J.*, 1950, 2728). The silver salt of the acid (IV) furnished, by the action of bromine in carbon tetrachloride (cf. Kleinberg, *Chem. Reviews*, 1947, **40**, 386), (−)-1-bromo-2 : 6-dimethylheptane (V) which by condensation with ethyl methylmalonate, followed by hydrolysis and decarboxylation of the product, afforded (−)-2 : 4 : 8-trimethylnonanoic acid (VI) having $[\alpha]_D$ −3·8°. [A new asymmetric centre at $C_{(2)}$ resulted from these processes.]

An alternative route tried was from active 4 : 8-dimethylnon-7-en-2-ol (VII), obtainable from (+)-citronellal by reaction with methylmagnesium iodide (Rupe, Pfeiffer, and Splittgerber, *Ber.*, 1907, **40**, 2813). This was converted, on hydrogenation followed by treatment of the resulting (−)-4 : 8-dimethylnonan-2-ol with hydrobromic acid, into (−)-1 : 3 : 7-trimethyloctyl bromide (VIII) which by carboxylation of the derived Grignard compound afforded (VI) in low yields.

(VII) $CH_3{\cdot}CMe{:}CH{\cdot}[CH_2]_2{\cdot}CHMe{\cdot}CH_2{\cdot}CHMe{\cdot}OH$ $CH_3{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CHMe{\cdot}CH_2{\cdot}CHMeBr$ (VIII)

(−)-2 : 5 : 9-Trimethyldecanoic acid (IX), $[\alpha]_D$ −0·1°, was readily obtained by a malonic ester condensation employing the bromide (II) and ethyl methylmalonate.

(IX) $CH_3{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}CHMe{\cdot}CO_2H$

The acids were brominated in the presence of red phosphorus (Hell–Volhard–Zelinsky method), and the resulting α-brominated acid bromides converted into the methyl esters by the action of dry methanol. Dehydrobromination of these bromo-esters was then examined. In the case of the bromo-ester derived from (−)-2 : 4 : 8-trimethylnonanoic acid (VI) the action of alcoholic potassium hydroxide afforded an optically inactive material (light absorption : max., 2170 Å; log ε, 3·58) which, as will be shown in a later paper, is probably a mixture of unsaturated acids with an α-hydroxy-acid. However, refluxing the bromo-ester with anhydrous pyridine yielded methyl (−)-2 : 4 : 8-trimethylnon-2-enoate (X; R = Me), $[\alpha]_D$ −21·3°, exhibiting an absorption maximum at 2170 Å (log ε, 4·08). A similar dehydrobromination of the bromo-ester from (−)-2 : 5 : 9-trimethyldecanoic acid (IX) by means of pyridine furnished methyl (−)-2 : 5 : 9-trimethyldec-2-enoate (XI; R = Me), $[\alpha]_D$ −0·1°, having an absorption maximum at 2180 Å (log ε, 3·92). In a comparative experiment, pyridine dehydrobromination of methyl (+)-2-bromo-3 : 7-dimethyloctanoate (from IV) also readily yielded the αβ-unsaturated ester (log ε, 4·10 at 2190 Å). In contrast to the preceding examples, (−)-4 : 8-dimethylnonanoic acid (III) by an analogous dehydrobromination of its bromo-ester with pyridine gave only a tar which was insoluble in ether.

The main interest of the above results lies in the demonstration that the optical rotation of (−)-2 : 4 : 8-trimethylnonanoic acid (VI), with an asymmetric centre at C_γ, is greatly increased on introduction of an αβ-double bond, whereas there is no such increase on introducing the αβ-double bond into (−)-2 : 5 : 9-trimethyldecanoic acid (IX). If it is assumed that racemization did not take place in the latter case, the comparison already indicates that the decrease in the optical rotations of the αβ-unsaturated acids from tubercle bacilli on hydrogenation must be due to the presence of an asymmetric centre in the γ-position of these acids. The degradative studies already mentioned (Polgar and Robinson, *loc. cit.* and forthcoming publication) have confirmed this and also shown that

one of these acids, termed mycolipenic acid-I, is 2 : 4 : 6-trimethyltetracos-2-enoic acid (XII). It thus contains the grouping $-CHMe\cdot CH{:}CMe\cdot CO_2H$ present in the synthetic acid (X; R = H). The synthesis of the latter, therefore, also indicates a possible route to the optically active natural substance.

(X) $CH_3\cdot CHMe\cdot[CH_2]_3\cdot CHMe\cdot CH{:}CMe\cdot CO_2R$ $CH_3\cdot CHMe\cdot[CH_2]_3\cdot CHMe\cdot CH_2\cdot CH{:}CMe\cdot CO_2R$ (XI)

$CH_3\cdot[CH_2]_{17}\cdot CHMe\cdot CH_2\cdot CHMe\cdot CH{:}CMe\cdot CO_2H$ (XII)

A feature of interest is the presence in the above acids (X) and (XII) of a three-carbon tautomeric system with an asymmetric centre adjacent to the αβ-double bond. It is evident that if at any time by tautomeric displacement of the double bond the corresponding βγ-unsaturated form were to be formed, racemization would necessarily result. When, however, methyl (−)-2 : 4 : 8-trimethylnon-2-enoate (X; R = Me) was hydrolysed by refluxing it for several hours with alcoholic potassium hydroxide, the acid was obtained with $[\alpha]_D$ −24·6° and there was no loss in rotatory power when it was further heated with an excess of alkali. This indicates much hindrance to the tautomeric mobility of the system $-CHMe\cdot CH{:}CMe\cdot CO_2H$. A similarly restricted tautomeric mobility has already been observed by Kon, Linstead, and their collaborators (*J.*, 1931, 1411; 1932, 2452, 2454) with αβ-dialkyl-substituted αβ- or βγ-unsaturated acids (*e.g.*, 2-ethyl-3-methylhex-2-enoic acid remains almost unchanged by prolonged boiling with an excess of aqueous potash).

It is of interest that ethyl (−)-2-carbethoxy-4 : 8-dimethylnonanoate (XIII), $[\alpha]_D$ −2·6°, obtained from (III) by way of the α-bromo- and the α-cyano-ester, on dehydrobromination of its α-bromo-derivative with pyridine gave an unsaturated product having a low extinction coefficient (log ε, 3·58 at 2190 Å) and no measurable rotation. This appears consistent with earlier findings that in such three-carbon tautomeric systems a γ-alkyl substituent favours the βγ-unsaturated form (Goldberg and Linstead, *J.*, 1928, 2343) and a second carbethoxyl grouping at the α-carbon atom, while favouring αβ-unsaturation, also tends to promote the tautomeric mobility of the system (Kon and Speight, *J.*, 1926, 2727).

During this work ethyl (−)-3-hydroxy-2 : 3 : 5 : 9-tetramethyldecanoate (XIV) has also been prepared by a Reformatsky reaction from (+)-4 : 8-dimethylnonan-2-one, the latter having been obtained from (−)-4 : 8-dimethylnonan-2-ol on oxidation with chromic acid. Dehydration of the hydroxy-ester (XIV) by phosphorus oxychloride (cf. Kon and Nargund, *J.*, 1932, 2461) gave an unsaturated ester containing only a small proportion of the αβ-unsaturated form (log ε, 3·45 at 2100 Å).

$CH_3\cdot CHMe\cdot[CH_2]_3\cdot CHMe\cdot CH_2\cdot CH(CO_2Et)_2$ (XIII)

$CH_3\cdot CHMe\cdot[CH_2]_3\cdot CHMe\cdot CH_2\cdot CMe(OH)\cdot CHMe\cdot CO_2Et$ (XIV)

Experimental

Ultra-violet absorption spectra were determined in methanol. We are indebted to Dr. F. B. Strauss for the measurements. Optical rotations were determined in 0·5-dm. tubes. M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss.

(+)-3 : 7-*Dimethyloctanoic Acid* (IV).—To a rapidly stirred solution of (+)-3 : 7-dimethyloctan-1-ol (I) (30 g.; $[\alpha]_D$ +3·5°, obtained by catalytic hydrogenation of commercial citronellol, $[\alpha]_D$ +3·7°) in acetone (100 c.c.) was added dropwise a solution of chromium trioxide (40 g.) in water (68 c.c.) and concentrated sulphuric acid (12 c.c.) during 75 minutes at such a rate that the temperature was maintained at 40—60°. The mixture was then diluted with water and extracted with ether from which the acidic fraction was removed by 10% sodium hydroxide solution. Acidification of the alkaline extract and isolation by means of ether afforded (+)-3 : 7-dimethyloctanoic acid (14·4 g., 44%), b. p. 139—141°/15 mm., d_4^{17} 0·880, $[\alpha]_D^{17}$ +4·2° (homog.) (Found : C, 70·0; H, 11·3. Calc. for $C_{10}H_{20}O_2$: C, 69·8; H, 11·6%). Three other runs, using the same quantities, were worked up together, yielding 54 g. (55%) of the acid.

3 : 7-*Dimethyloct-2-enoic Acid*.—To a mixture of (+)-3 : 7-dimethyloctanoic acid (50 g.) and red phosphorus (9·02 g.) was added dropwise dry bromine (182 g.) during 30 minutes while the mixture was stirred at 90° (bath-temp.). After a further 15 hours' heating at 90°, the mixture was cooled and dry methanol (60 c.c.) introduced during 1 hour. The product was kept at room

temperature for 1 hour, then refluxed for 2 hours. Dilution with water and extraction with ether afforded the crude bromo-ester. This ester (2 g.) and pyridine (4 c.c.) were refluxed for 10 hours. The mixture was then cooled and poured into dilute hydrochloric acid, and *methyl* 3 : 7-*dimethyloct-2-enoate* isolated, with ether, as an oil (0·6 g.), b. p. 115°/15 mm. (Found : C, 71·1; H, 10·9. $C_{11}H_{20}O_2$ requires C, 71·7; H, 10·9%). Light absorption : Max., 2190 Å; log ε, 4·10.

The foregoing ester (0·4 g.) was refluxed with potassium hydroxide (0·5 g.) in water (1 c.c.) and ethanol (4 c.c.) for 3 hours. Dilution with water, acidification, and isolation with ether afforded 3 : 7-*dimethyloct-2-enoic acid*, b. p. 140°/15 mm. Light absorption : Max., 2180 Å; log ε, 4·04. The S-*benzylthiuronium* salt crystallized from aqueous ethanol in leaflets, m. p. 149° (Found : C, 63·7; H, 8·3; N, 8·1. $C_{18}H_{28}O_2N_2S$ requires C, 64·3; H, 8·3; N, 8·3%).

(−)-1-*Bromo*-3 : 7-*dimethyloctane* (II).—(+)-3 : 7-Dimethyloctan-1-ol (117 g.) was refluxed with hydrobromic acid (48%; 277 c.c.) and concentrated sulphuric acid (55·5 c.c.) for 3·5 hours. The mixture was then poured into water and extracted with ether. Evaporation of the ether afforded the bromide, b. p. 102—107°/15 mm. (91 g.), d_4^{20} 1·05, $[\alpha]_D^{20}$ −4·6° (homog.).

(−)-4 : 8-*Dimethylnonanoic Acid* (III).—A Grignard reagent was prepared from the preceding bromide (25 g.) and magnesium (3 g.) in ether (50 c.c.) in the usual fashion. Solid carbon dioxide was added to the cooled solution, and the mixture set aside at room temperature for 2 hours. It was then poured into dilute hydrochloric acid, and the ethereal layer washed with water and extracted with 10% aqueous sodium hydroxide (4 × 25 c.c.). The product obtained on acidification of the alkaline extracts was isolated with ether and distilled, affording (−)-4 : 8-dimethylnonanoic acid (9·3 g.), b. p. 152°/12 mm., d_{24}^{24} 0·879, $[\alpha]_D^{17}$ −1·0° (homog.) (Found : C, 70·9; H, 12·1. Calc. for $C_{11}H_{22}O_2$: C, 71·0; H, 11·8%). Von Braun and Kaiser, *Ber.*, 1923, **56**, 2268, record $[\alpha]_D$ −0·58°.

Methyl (−)-2-*Bromo*-4 : 8-*dimethylnonanoate*.—The preceding acid (8 g.) was brominated as before (28 g. of bromine, 1·33 g. of red phosphorus). Reaction of the resulting acid bromide with dry methanol (10 c.c.) in the manner already described gave *methyl* (−)-2-*bromo*-4 : 8-*dimethylnonanoate* which distilled as an oil (10 g.), b. p. 135—138°/12 mm., d_4^{22} 1·125, $[\alpha]_D^{18}$ −6·5° (homog.) (Found : C, 51·65; H, 8·1; Br, 28·6. $C_{12}H_{23}O_2Br$ requires C, 51·6; H, 8·2; Br, 28·7%).

Attempted Dehydrobromination of Methyl (−)-2-*Bromo*-4 : 8-*dimethylnonanoate*.—The preceding bromo-ester was refluxed with a large excess of anhydrous pyridine for 5 hours. On pouring of the solution into dilute hydrochloric acid a tar was obtained which was insoluble in ether; no ether-soluble product was found. The same result was obtained on refluxing the bromo-ester (2 g.) with pyridine (4 c.c.) for 30 minutes.

(−)-1-*Bromo*-2 : 6-*dimethylheptane* (V).—To a solution of (+)-3 : 7-dimethyloctanoic acid (27 g.) in a slight excess of aqueous ammonia was added a solution of silver nitrate (27·2 g.) in water (20 c.c.), and the mixture heated at 80° for 30 minutes. The precipitated silver salt was collected, and washed with aqueous ammonia, water, and finally repeatedly with acetone. It was dried at 100° for 30 minutes. A suspension of the salt in carbon tetrachloride (50 c.c.) was stirred and cooled with running water while bromine (8 c.c.) was added dropwise during 30 minutes; the mixture was then refluxed on the steam-bath for 1 hour. After filtration, the solution was evaporated, and the residue taken up in ether and extracted with 10% sodium hydroxide solution to remove unchanged acid (4 g.). Distillation of the ethereal solution afforded (−)-1-*bromo*-2 : 6-*dimethylheptane* (16·5 g., 55%), b. p. 82—85°/12 mm., d_4^{20} 1·065, $[\alpha]_D^{15}$ −0·4° (homog.) (Found : C, 51·7; H, 9·25; Br, 38·6. $C_9H_{19}Br$ requires C, 52·2; H, 9·2; Br, 38·65%).

(−)-4 : 8-*Dimethylnonan*-2-*ol*.—(−)-4 : 8-Dimethylnon-7-en-2-ol (VII) was prepared from (+)-citronellal, $[\alpha]_D^{15}$ +10·8°, according to the procedure of Rupe *et al.* (*loc. cit.*) except that the ethereal extract of the crude product was washed with a concentrated solution of sodium hydrogen sulphite to remove unchanged citronellal. Evaporation and distillation of the residual product afforded (−)-4 : 8-dimethylnon-7-en-2-ol, b. p. 130—135°/25 mm., $[\alpha]_D^{15}$ −0·8° (homog.) (Rupe *et al.*, starting from citronellal, $[\alpha]_D$ +12·3°, record $[\alpha]_D$ +0·55°). This was hydrogenated in ethanol (100 g. in 400 c.c.) in the presence of Raney nickel at 50°/50 atm., to give (−)-4 : 8-*dimethylnonan*-2-*ol*, $[\alpha]_D^{15}$ −4·7° (homog.) (Found : C, 76·7; H, 14·0. $C_{11}H_{24}O$ requires C, 76·8; H, 14·0%).

(−)-1 : 3 : 7-*Trimethyloctyl Bromide* (VIII).—The preceding alcohol (50 g.) was refluxed with hydrobromic acid (48%; 109 c.c.) and concentrated sulphuric acid (5 c.c.). After 1 hour a further quantity (5 c.c.) of concentrated sulphuric acid was added and refluxing continued for a further 3 hours. Dilution with water and isolation with ether afforded, in addition to an

unsaturated fraction, b. p. 75—102°/15 mm. (23·5 g.), (−)-1 : 3 : 7-*trimethyloctyl bromide* (25·5 g.), b. p. 103—108°/15 mm., $[\alpha]_D^{15}$ −4·4° (homog.) (Found : Br, 33·2. $C_{11}H_{23}Br$ requires Br, 34·0%). The procedure is obviously unsatisfactory for the preparation of bromides from secondary alcohols.

(−)-2 : 4 : 8-*Trimethylnonanoic Acid* (VI).—(a) *From* (−)-1-*bromo*-2 : 6-*dimethylheptane*. To an ethanolic solution of sodium ethoxide, obtained from sodium (3·2 g., 1·8 mols.) and ethanol (100 c.c.), were added ethyl methylmalonate (26·9 g., 2 mols.; Blatt, *Org. Synth.*, Coll. Vol. II, 1943, pp. 272, 279) and some sodium iodide, and the mixture was heated to boiling under reflux. 1-Bromo-2 : 6-dimethylheptane (16 g.) was then introduced dropwise during 15 minutes and refluxing continued for 6 hours. The bulk of the ethanol was evaporated, a solution of sodium hydroxide (24 g.) in water (30 c.c.) added to the residue, and the mixture refluxed for 6 hours. Decarboxylation (150—170°, 30 minutes) of the liberated acid furnished (−)-2 : 4 : 8-*trimethylnonanoic acid* (9 g.), b. p. 160°/15 mm., d_4^{22} 0·879, $[\alpha]_D^{15}$ −3·8° (homog.), n_D^{24} 1·4393 (Found : C, 71·5; H, 12·1. $C_{12}H_{24}O_2$ requires C, 72·0; H, 12·0%).

(b) *From* (−)-1 : 3 : 7-*trimethyloctyl bromide*. A Grignard reagent from this bromide (20 g.) and magnesium (2·2 g.) in ether (75 c.c.) was carboxylated by a large excess of solid carbon dioxide and the mixture kept for 2 hours. The Grignard complex was then decomposed by means of dilute hydrochloric acid, and the ether layer extracted with 10% aqueous sodium hydroxide. Acidification of the alkaline extract and isolation with ether, followed by distillation, gave (−)-2 : 4 : 8-trimethylnonanoic acid (3·5 g.), b. p. 160°/15 mm., $[\alpha]_D^{15}$ −3·5° (*c* 25 in Et_2O), n_D^{24} 1·4385 (Found : C, 72·35; H, 12·15%).

(−)-2 : 4 : 8-*Trimethylnon*-2-*enoic Acid* (X; R = H).—(−)-2 : 4 : 8-Trimethylnonanoic acid (9 g.) was heated with bromine (30 g.) in the presence of red phosphorus (1·35 g.) at 90° for 10 hours in the manner already described. Dry methanol (15 c.c.) was then slowly added and, after 2 hours' refluxing of the mixture, the resulting methyl ester was isolated with ether. The bromo-ester (7 g.) was refluxed with anhydrous pyridine (15 c.c.) for 15 hours. Dilution with water, extraction with ether, and distillation furnished *methyl* (−)-2 : 4 : 8-*trimethylnon*-2-*enoate* (X; R = Me) (4·1 g.), b. p. 113—116°/10 mm., d_4^{22} 0·873, $[\alpha]_D^{14}$ −21·3° (homog.), n_D^{19} 1·4452 (Found : C, 73·1; H, 11·3. $C_{13}H_{24}O_2$ requires C, 73·6; H, 11·3%). Light absorption : Max., 2170 Å; log ε, 4·08.

The foregoing methyl ester (1 g.) was refluxed with a solution of potassium hydroxide (0·75 g.) in ethanol (13 c.c.) and water (2 c.c.) for 5 hours. Extraction of the acidified mixture with ether and distillation gave (−)-2 : 4 : 8-*trimethylnon*-2-*enoic acid* (X; R = H) as an oil (0·8 g.), $[\alpha]_D^{18}$ −24·6° (*c*, 10 in Et_2O) (Found : C, 72·7; H, 11·1. $C_{12}H_{22}O_2$ requires C, 72·7; H, 11·1%). Light absorption : Max., 2170 Å; log ε, 4·05. No change in the optical rotation was observed on heating the acid with 10% alcoholic potassium hydroxide for 5 hours. The S-*benzylthiuronium* salt crystallized from aqueous ethanol in needles, m. p. 132—133° (Found : C, 65·7; H, 9·0; N, 7·6. $C_{20}H_{32}O_2N_2S$ requires C, 65·9; H, 8·8; N, 7·7%).

On refluxing of the above bromo-ester (2 g.) with a solution of potassium hydroxide (2 g.) in ethanol (9 c.c.) and water (1 c.c.) for 3 hours the resulting acid (Light absorption : Max., 2170 Å; log ε, 3·58) exhibited no measurable rotation.

(−)-2 : 5 : 9-*Trimethyldecanoic Acid* (IX).—(−)-1-Bromo-3 : 7-dimethyloctane (91 g.) was added to the sodio-derivative of ethyl methylmalonate, obtained from sodium (13·3 g., 1·4 mols.), ethanol (500 c.c.), and ethyl methylmalonate (108 g., 1·5 mols.), during 45 minutes while the mixture was refluxed; heating was then continued for 15 hours. *Ethyl* (−)-2-*carbethoxy*-2 : 5 : 9-*trimethyldecanoate*, isolated in the known manner, distilled as an oil (72 g.), b. p. 189—190°/15 mm., $[\alpha]_D^{20}$ −1·16° (homog.) (Found : C, 69·3; H, 10·9. $C_{18}H_{34}O_4$ requires C, 68·8; H, 10·8%). Hydrolysis with ethanolic potassium hydroxide (33 g., in 20 c.c. of water and 100 c.c. of ethanol), followed by acidification and decarboxylation (160—170°, 2 hours), furnished (−)-2 : 5 : 9-*trimethyldecanoic acid*, b. p. 177—178°/20 mm., as a pale yellow oil (45 g.), $[\alpha]_D^{23}$ −0·1° (homog.) (Found : C, 73·3; H, 12·4. $C_{13}H_{26}O_2$ requires C, 72·9; H, 12·15%).

(−)-2 : 5 : 9-*Trimethyldec*-2-*enoic Acid* (XI; R = H).—The preceding acid (20 g.) was heated with bromine (58 g.) in the presence of red phosphorus (3 g.) for 20 hours, as already described for similar cases, and the resulting crude acid bromide (24·8 g.) converted into the methyl ester by means of methanol (30 c.c.). A 15-g. portion of this ester was refluxed with anhydrous pyridine (30 c.c.) for 15 hours. *Methyl* (−)-2 : 5 : 9-*trimethyldec*-2-*enoate* (XI; R = Me), isolated as before, was an oil (7·8 g.), b. p. 137—139°/18 mm., $[\alpha]_D^{15}$ −0·1° (homog.) (Found : C, 74·8; H, 11·7. $C_{14}H_{26}O_2$ requires C, 74·3; H, 11·5%). Light absorption : Max., 2180 Å; log ε, 3·92.

The corresponding *acid*, obtained by hydrolysis with alcoholic potassium hydroxide, had

b. p. 172°/15 mm. (Found : C, 73·3; H, 11·6. $C_{13}H_{24}O_2$ requires C, 73·6; H, 11·3%). The acid had no measurable rotation in ether (*c*, 40). Its S-*benzylthiuronium* salt crystallized from aqueous ethanol in needles, m. p. 126° (Found : C, 67·2; H, 9·2; N, 7·7. $C_{21}H_{34}O_2N_2S$ requires C, 66·7; H, 9·0; N, 7·4%).

Ethyl (−)-2-*Carbethoxy*-4 : 8-*dimethylnonanoate* (XIII).—Methyl (−)-2-bromo-4 : 8-dimethylnonanoate (6 g.) was heated under reflux on a steam-bath with a solution of potassium cyanide (3·5 g.) in ethanol (25 c.c.) and water (5 c.c.) for 2 hours. Acidification with hydrochloric acid and extraction of the product with ether afforded the crude cyano-acid (4·8 g.) as a dark oil. This was heated under reflux with ethanol (20 c.c.) and concentrated sulphuric acid (7 c.c.) for 15 hours. After dilution with water the product was collected with ether and distilled. *Ethyl* (−)-2-*carbethoxy*-4 : 8-*dimethylnonanoate* was obtained as an oil (3·2 g.), b. p. 175—180°/18 mm., $[\alpha]_D^{18}$ −2·6° (homog.) (Found : C, 67·6; H, 10·65. $C_{16}H_{30}O_4$ requires C, 67·1; H, 10·5%).

Bromination of Ethyl (−)-2-*Carbethoxy*-4 : 8-*dimethylnonanoate and Dehydrobromination of the* α-*Bromo-ester*.—Bromine (1·85 g.) in carbon tetrachloride (5 c.c.) was slowly added during 30 minutes to a boiling solution of ethyl (−)-2-carbethoxy-4 : 8-dimethylnonanoate (3·1 g.) in carbon tetrachloride (10 c.c.). The solution was refluxed for a further 6 hours; the carbon tetrachloride and excess of bromine were then distilled off under reduced pressure. The residual pale oil (3·9 g.) was refluxed in anhydrous pyridine (10 c.c.) for 15 hours. The mixture was then poured into dilute hydrochloric acid and the product isolated with ether. The resulting unsaturated *ester* distilled as a pale yellow oil (0·9 g.), b. p. 175°/18 mm. (Found : C, 67·1; H, 10·2. $C_{16}H_{28}O_4$ requires C, 67·6; H, 9·9%). Light absorption : Max., 2190 Å; log ε, 3·58. The product had no measurable rotation (*c* = 10 in Et_2O).

(+)-4 : 8-*Dimethylnonan*-2-*one*.—(−)-4 : 8-Dimethylnonan-2-ol (50 g.) was added with stirring during 1 hour to a solution of sodium dichromate (28·5 g.) in water (190 c.c.) and concentrated sulphuric acid (21 c.c.). The temperature was then raised to 90° and stirring continued for a further 2 hours. The mixture was then diluted with water and the product isolated by means of ether. Distillation gave (+)-4 : 8-*dimethylnonan*-2-*one* (45 g.), b. p. 87—92°/10 mm., $[\alpha]_D^{15}$ +2·1° (homog.) (Found : C, 77·9; H, 12·9. $C_{11}H_{22}O$ requires C, 77·7; H, 12·9%). Its *semicarbazone* crystallized from methanol in needles, m. p. 98° (Found : C, 63·2; H, 10·7; N, 19·0. $C_{12}H_{25}ON_3$ requires C, 63·45; H, 11·0; N, 18·5%).

Ethyl (−)-3-*Hydroxy*-2 : 3 : 5 : 9-*tetramethyldecanoate* (XIV).—A mixture of (+)-4 : 8-dimethylnonan-2-one (20 g.) and ethyl 2-bromopropionate (42·6 g.) in benzene (250 c.c.) was added dropwise during 2 hours to a suspension of zinc dust (16 g.) in benzene (50 c.c.) with stirring and heating under reflux. After a further 2 hours' refluxing the product was poured into dilute hydrochloric acid and worked up in the usual manner. On distillation *ethyl* (−)-3-*hydroxy*-2 : 3 : 5 : 9-*tetramethyldecanoate* (12·9 g.) was obtained, b. p. 168—172°/25 mm., $[\alpha]_D^{15}$ −0·8° (homog.) (Found : C, 70·4; H, 11·8. $C_{16}H_{32}O_3$ requires C, 70·6; H, 11·8%).

Dehydration of Ethyl (−)-3-*Hydroxy*-2 : 3 : 5 : 9-*tetramethyldecanoate*.—A solution of the preceding ester (12·8 g.) in benzene (45 c.c.) was refluxed with phosphorus oxychloride (7·7 g.) for 1·5 hours. The mixture was poured into water and the benzene layer washed repeatedly with dilute aqueous sodium hydroxide. Distillation gave the unsaturated *ester* (8·2 g.), b. p. 139—144°/12 mm., $[\alpha]_D^{17}$ −2·1° (homog.) (Found : C, 76·1; H, 11·9. $C_{16}H_{30}O_2$ requires C, 75·6; H, 11·8%). Light absorption : Max., 2100 A; log ε, 3·45. The corresponding *acid*, obtained by refluxing of the ester (2·9 g.) with potassium hydroxide (5 g.) in water (5 c.c.) and ethanol (25 c.c.) for 5 hours, had $[\alpha]_D^{17}$ −4·2° (*c* = 24 in Et_2O) (Found : C, 74·4; H, 11·7. $C_{14}H_{26}O_2$ requires C, 74·3; H, 11·5%). Light absorption : Max., 2100 Å; log ε, 3·43. Its S-*benzylthiuronium* salt crystallized from aqueous ethanol in leaflets, m. p. 113—114° (Found : C, 67·9; H, 9·05; N, 7·0. $C_{22}H_{36}O_2N_2S$ requires C, 67·35; H, 9·2; N, 7·1%).

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27. *The Oxidation of Monoethenoid Fatty Acids and Esters. Catalytic Oxidation of Elaidic Acid, Methyl Elaidate, and n-Propyl Elaidate. The Oxidation Products.*

By J. H. Skellon and M. N. Thruston.

The products of oxidation of highly purified elaïdic acid and its methyl and *n*-propyl esters by gaseous oxygen have been semi-quantitatively resolved. Whilst dimerisation may occur on prolonged oxidation at 120°, in short, controlled catalytic oxidations pure elaidic acid and its esters behave similarly to the *cis*-acid. The primary reaction is a chain-reaction involving the formation of isomeric hydroperoxides, and is followed by secondary breakdown to unsaturated ketones, acidic fission compounds, and neutral saturated substances. The production of carbon dioxide and water are due to this secondary breakdown, which at 120° commences at an early stage. At 98°, only small amounts of elaidic acid epoxides were isolated, and there was little or no evidence to indicate that such compounds are formed in the initial stages of autoxidation.

The mechanism of catalytic oxidation of monoethenoid fatty acids and esters is discussed.

Skellon and Thruston (*J.*, 1949, 1626) showed that at 85—120° maximum peroxidation of elaidic acid and its methyl and *n*-propyl esters occurred with little or no dimerisation. Investigation of the numerous products of controlled autoxidations at a stage where minimum secondary degradation occurs is now described.

Farmer (*J.*, 1942, 121) put forward a radical chain reaction, later extended (*Trans. Faraday Soc.*, 1946, **42**, 233) to postulate universal initial attack by oxygen at the ethylenic linkage, but only to an extent sufficient to initiate the chain reaction. Gunstone and Hilditch (*J.*, 1946, 1022) suggested primary entry of oxygen at the ethylenic linkage with subsequent migration of the ethenoid bond owing to induced polar effects. Ross, Gebhardt, and Gerecht (*J. Amer. Chem. Soc.*, 1949, **71**, 282), from a study of autoxidations of methyl oleate at 35° in the presence of ultra-violet light, suggested that the initial point of entry of oxygen was at the α-methylene group. According to Ellis (*Biochem. J.*, 1950, **46**, 129) autoxidation may involve initial formation of olefinic keto-acids with secondary degradation to hydroperoxides. Modern views have been reviewed by Hilditch (*Nature*, 1950, **166**, 558) who stressed the necessity for purity of initial starting materials: thus, linoleate containing the pentadiene system will catalyse oxidation of mono-ethenoid fatty acids. Below 50°, it is probable that attack occurs at the α-methylene group and at higher temperatures direct union between oxygen and the double bond proceeds rapidly.

The highly purified oleic acid used in the present work was isolated from saponified high-grade olive oil by low-temperature crystallisation from acetone. Although in our previous work a pure acid was obtained by the lead–lithium salt method (Skellon, *J. Soc. Chem. Ind.*, 1931, **50**, 130T) it was considered that low-temperature separation might afford less likelihood of premature oxidation. After elaidinisation and esterification, the pure compounds were catalytically oxidised with uranium elaidate as catalyst (Skellon and Spence, *ibid.*, 1948, **67**, 365) and high oxygen dispersion in order to achieve rapid peroxidation with the minimum of secondary breakdown. It was apparent that such secondary decomposition occurrred more readily at high temperature. During oxidation of elaidic acid, carbon dioxide was not observed until after 5 hours, when peroxidation had reached 0·5%, whilst water formed amounted to one mole per mole of acid. The degree of fission, however, amounted to only approx. 0·1 carbon atom per molecule. There was no evidence that the small yield of epoxide obtained was a *primary* product of oxidation. The nature of some of the low-temperature products indicated occurrence of slight dimerisation above 100°. Strong alkaline hydrolysis destroyed peroxide, yielding unsaturated resinous complexes of low ketone content together with dihydroxystearic acid, the latter not being present in the original oxidised acid.

In autoxidation of the esters, two temperatures were used. At 120°, carbon dioxide was evolved at once, whereas at 98° no carbon dioxide was evolved for 10 hours. As with elaidic acid, unchanged ester was detected at the lower temperature, though not at 120°. Similarly 9 : 10-dihydroxystearic acid, m. p. 132°, was produced only after hydrolysis. Infra-red analysis of oxidation products (freed from acidic degradation substances) indicated an increase in asymmetry due possibly to migration of the ethylenic linkage.

The presence of dihydroxystearic acid, invariably resulting from strong alkaline hydrolysis of the oxidation products, appeared to indicate that the main reactive centres are seated at $C_{(9)}$ and $C_{(10)}$; the acid would be produced on decomposition of hydroperoxides, on breakdown of dimeric complexes, or on hydrolysis of an epoxide, although the epoxides are fairly resistant to hydrolysis.

The degree of peroxidation was 33% for methyl elaidate at 98° and 10—15% for the elaidic acid at 98° and for propyl elaidate at 120° but, as the oxidations were arrested soon after the stage of maximum peroxidation, pronounced fission was not to be expected (10—15% was found). The acids produced were: azelaic and suberic (from elaidic acid); azelaic, nonanoic, and decanoic (from methyl elaidate); and azelaic and decanoic (from *n*-propyl elaidate). It therefore seemed likely that attack was initiated at one of the forms:

$CH_3\cdot[CH_2]_8\cdot CH{:}CH\cdot[CH_2]_6\cdot CO_2R$ $CH_3\cdot[CH_2]_7\cdot CH{:}CH\cdot[CH_2]_7\cdot CO_2R$ $CH_3\cdot[CH_2]_6\cdot CH{:}CH\cdot[CH_2]_8\cdot CO_2R$

Hydroperoxidation could therefore occur at $C_{(8)}$, $C_{(9)}$, $C_{(10)}$, and $C_{(11)}$, with production of following degradation products: (*a*) at $C_{(9,8)}$: decanoic, heptanoic, nonanoic, and suberic acid; (*b*) at $C_{(11,10)}$: sebacic, octanoic, heptanoic, and azelaic acid. Both oxidised esters yielded comparatively large amounts of decanoic acid. These results indicated that the primary reaction involves hydroperoxide formation which may occur at $C_{(8)}$, $C_{(9)}$, $C_{(10)}$, or $C_{(11)}$; secondary fission products are then formed together with long-chain unsaturated ketonic compounds.

Mild hydrolysis of the oxidised esters, followed by isolation of a volatile oil as described by Ellis (*Biochem. J.*, 1950, **46**, 129), was carried out, but no positive evidence was obtained indicative of the presence of α- or β-unsaturated keto-acids. During autoxidations of oleic and elaidic acid at about 65° Ellis (*loc. cit.*) suggested that the α- and β-unsaturated keto-acids (I) and (II) were formed in significant amount. Mild hydrolysis of (I) yields azelaic semialdehyde and heptyl methyl ketone, and (II) gives nonaldehyde and 8-oxo-octane-1-carboxylic acid, products which afford evidence of the presence of the original unsaturated keto-acids.

(I) $CH_3\cdot[CH_2]_6\cdot CO\cdot CH{:}CH\cdot[CH_2]_7\cdot CO_2H$ $CH_3\cdot[CH_2]_7\cdot CH{:}CH\cdot CO\cdot[CH_2]_6\cdot CO_2H$ (II)

The volatile oils recovered from autoxidised elaidic esters at 85—120° were neutral and in the case of the *n*-propyl derivative yielded a ketone with an approximate molecular weight of 240 and a CO content of 9·3%.

Infra-red spectra of some of the products (see p. 142) appeared to substantiate the experimental evidence already adduced. Symmetry of the molecule about the double bond was apparently disturbed by oxidation, as shown by the appearance of a band near 6·1 μ, which was rather more pronounced in the oils *before* subjection to attempted ketone removal by Ellis's method (*loc. cit.*). The disturbance of symmetry might well indicate bond shift in peroxidation such as would take place on a direct attack at the unsaturated centres.

The *trans*-configuration of the compounds as a whole was apparently unaffected, as the characteristic band at 10·37 μ was clearly visible (Cross, Richards, and Willis, Faraday Soc. Symposium, Sept., 1945).

The oil (V) recovered from oxidised propyl oleate after cold alcoholic treatment of the neutral product gave a prominent band at 9·55 μ (which might possibly be due to a hydroxy-group), and another about 11·4 μ. The infra-red curves for oxidised propyl elaidate gave no positive evidence of presence of epoxides; the results of chemical analysis had also given no yield of epoxide in oxidised propyl oleate, but from oxidised elaidic acid and methyl elaidate 3—5% of epoxides had been recovered.

These results generally confirmed chemical evidence supporting the view that migration of the ethylenic linkage occurs, and that at temperatures above 100° initial attack by oxygen at the α-methylenic groups seems unlikely. Thermal catalytic oxidation of elaidic acid and its esters appears, therefore, to take the following course: (1) The oxidations are probably chain reactions initiated by $-O{\cdot}OH$ (Gibson, *J.*, 1948, 2275) with direct attack at, and subsequent displacement of, the ethylenic linkage:

$$-\overset{11}{C}H_2-\overset{10}{C}H=\overset{9}{C}H- \longrightarrow -\overset{11}{C}H_2-\overset{10}{C}H(O{\cdot}OH)-\overset{9}{C}H- \longrightarrow -\overset{11}{C}H=\overset{10}{C}H-\overset{9}{C}H(O{\cdot}OH)- + H$$

$$H^- + O_2 \longrightarrow HO{\cdot}O^-$$

The resulting hydroperoxides would be identical with those obtained either by assumption of initial loose complex formation, as suggested by Bergstrom (*Nature*, 1945, **156**, 717) or on the alternative theory of initial attack at an α-methylenic group (Farmer, *loc. cit.*). The presence of terminal alkyl groups undoubtedly favours hydroperoxide formation. (2) Decomposition of the hydroperoxide occurs at a rate depending on the external conditions, with formation of three main types of secondary oxidation products, in varying quantity: (*a*) Monomeric oily complexes (40—60% yield) containing ketonic groups, one possible structure for which was formerly suggested by Skellon (*J.*, 1948, 343). There is little or no evidence of dimerisation in catalytic oxidations below 100°. (*b*) Other secondary oxidation products formed without rupture of the carbon chain, *viz.*, epoxides (from elaidic acid and the lower esters) and volatile ketonic esters. Dihydroxystearic acid, however, is only recovered after powerful alkaline hydrolysis. (*c*) Scission products (monobasic and dibasic acids) which may result from hydroperoxide fission or from breakdown of the oily complexes.

Experimental

Preparation of Elaidic Acid by Low-temperature Crystallisation.—High-grade olive oil (500 g.) was saponified for 3 hours with potassium hydroxide (100 g.) in 95% alcohol (1 l.) and water (200 ml.). After removal of excess of alcohol and acidification the separated acids were washed six times with hot water (yield, 481 g.). These (250 g.) were dissolved in acetone (2500 ml.), cooled (½ hour) to −25° in solid carbon dioxide with stirring, and kept at −25° to −20° in a 1-gallon Dewar vessel for 4½ hours. The precipitate was filtered off at −15° to −18° and the filtrate cooled to −60° and filtered, after a few hours, at the pump (Smith, *J.*, 1939, 974). The insoluble material was dissolved in acetone (1500 ml.), and the whole cooled at −40° for 4 hours and filtered. The colourless solid was redissolved in acetone (1500 ml.), again cooled to −40°, and treated as before. The solid thus obtained (largely oleic acid, plus some saturated acids) was treated with alcohol (500 ml.) containing lead acetate (6 g.) and acetic acid (1—2 ml.). After boiling and cooling rapidly in nitrogen a small crop of lead salts was removed, and the filtrate freed from residual acetone *in vacuo*. After acidification, ether-extraction, and removal of traces of lead chloride, pure oleic acid was recovered by vacuum-distillation in nitrogen. It was converted into elaidic acid (*J.*, 1949, 1626), which, dried over ignited alumina *in vacuo* (1 week), had m. p. 43·7° ± 0·1° (Found: I.V., 88·7. Calc. for $C_{18}H_{34}O_2$: I.V., 90·1).

Catalytic Oxidations. General.—Pure dry oxygen at a known pressure was passed into the molten acid or ester contained in a round-bottomed Pyrex tube (5 × 1½″) fitted with a stopper through which passed a sintered-glass bubbler (for oxygen), a thermometer, a stoppered tube (for a sampling pipette), and an exit tube. The apparatus was immersed in a thermostatically controlled oil-bath, and exit gases were passed through a glass-stoppered weighed U tube and through saturated barium hydroxide solution. All oxidations were carried out in the presence of 0·05% of uranium as "uranium elaidate."

Elaidic Acid at 98°.—A stream of oxygen at 20 mm. pressure was passed into the acid (I.V., 88·2; acid val., 197; m. p. 43·6°; 30 g.) for 11 hours. Volatile product were first observed at 5 hours as a condensate (1·884 g.) in the U tube; after 5 hours 1·95 g. of barium carbonate were formed. Peroxide contents were:

Time (hr.)	1	2	3	5	7	10	11
Active O, %	0·140	0·217	0·256	0·508	0·678	0·648	0·625

The oxidised product [I.V., 39·6; acid val., 180; *M* (Rast), 324] (10 g.) was dissolved in acetone (100 ml.) and cooled overnight at −80°. After recrystallisation of the precipitate, the bulked filtrates were subjected to vacuum-distillation at low temperature, yielding a yellow oil (active O, 0·607%) (8·05 g.) and a white solid (A) [I.V., 54·5; *M* (Rast), 269; acid val., 190] (1·43 g.). The oil (7·75 g.) was further fractionated in acetone (40 ml.) at −20° (4 hours), giving a solid (active O, 0·285%; I.V., 43·0; acid val., 196) (0·127 g.). The filtrate at −40° gave a semi-solid material (1·70 g.) [active O, 0·313%; I.V., 33·1; *M* (Rast), 424; acid val., 170] and then at −80° gave a solid (0·616 g.) melting at room temperature [active O, 0·370%; I.V., 24·1; *M* (Rast), 352; acid val., 178]. The final filtrate gave a yellow oil (4·45 g.), n_D^{20} 1·4642 (active O, 0·689%; I.V., 36·3; *M* (Rast), 306; acid val., 157].

Solid A, when kept in aqueous alcohol overnight at 0°, afforded elaidic acid (0·57 g.; m. p. 43·8°) and there was recovered 0·57 g. of a solid, equiv. 285, after recrystallisation. The soluble material, when twice recrystallised from *n*-hexane, gave elaidic acid epoxide, m. p. 54·5° (lit., 55·5°) (Found: equiv., 301. Calc. for $C_{18}H_{34}O_3$: equiv., 298). The residue consisted of oily keto-derivatives. The original oxidised end-product contained no epoxide (Ellis's method, *Biochem. J.*, 1936, **30**, 753), but yielded small amounts of azelaic, m. p. 107° (Found: equiv., 98), and suberic acid, m. p. 140° (Found: equiv., 86·2. Calc. for $C_8H_{14}O_4$: equiv., 87·1).

Saponification of the original oxidation product (6·7 g.), acidification, and ether-extraction afforded insoluble dihydroxystearic acid (1·1 g.), m. p. 131° (lit., m. p. 132°) (Found: equiv., 316·4. Calc. for $C_{18}H_{36}O_4$: equiv., 316). From the ether-extract was recovered brown solid (4·9 g.), whence hot light petroleum (150 ml.; b. p. 40—60°) left an insoluble brown residue, which crystallised from benzene; recrystallisation of the resultant solid gave 0·05 g. of solid, having m. p. 100—103° (0·05 g.) and reducing Fehling's solution (Found: equiv., 298). The benzene filtrates yielded an orange viscous oil (1 g.) (Found: equiv., 217; I.V., 34·4; CO, 1·9%). The light petroleum filtrate at 0° gave a very small amount of dihydroxystearic acid and then, on evaporation to dryness and recrystallisation of the residue from aqueous alcohol (at 0°), a solid (B) (1·2 g.) which, after crystallisation from *n*-hexane, was identified as elaidic acid; the aqueous alcoholic filtrates from B contained a yellow oil (Found: CO, 1·4%).

Methyl Elaidate at 98°.—The ester (Skellon and Thruston, *loc. cit.*) was oxidised for 20 hours. Carbon dioxide was observed after 10 hours (1·38 g. of barium carbonate). 0·503 G. of volatile material was collected, from which 0·10 ml. of aldehydic or ketonic oil was isolated. Changes in peroxide oxygen content were:

Time (hr.)	3	8	13	19
Active O, %	0·439	1·08	1·31	1·46

n-*Propyl Elaidate at* 120°.—The ester (30 g.), n_D^{20} 1·4481 (Found: sap. val., 175·5. Calc. for $C_{20}H_{38}O_2$: sap. val., 173), was oxidised for 11 hours (2·05 g. of barium carbonate; 0·5417 g. of volatile product giving 0·10 ml. of aldehydic or ketonic oil). Changes in peroxide oxygen content were:

Time (hr.)	5	6	9	11
Active O, %	0·454	0·445	0·508	0·407

Detailed Analysis of the Oxidised Esters.—(a) *Resolution into acidic and neutral fractions.* The oxidation products of methyl elaidate (termed Me below) (10 g.) and propyl elaidate (termed Pr below) (15 g.) in ether (40 ml.) were extracted thrice with 20% sodium carbonate solution. After being washed with ether, the alkaline extracts were refluxed with 30% aqueous potassium hydroxide (50 ml.), and then recovered with ether. Me gave 1·40 g. (Found: I.V., 15·6; equiv., 167), and Pr 1·70 g. (Found: I.V., 20·6; equiv., 189) of brown acids. Recovery of the neutral oxidation products yielded pale oils (Me, 7·6; Pr, 11·6 g.).

(b) *Separation of the acidic products.* The acids were refluxed four times with light petroleum (b. p. 40—60°), and the concentrated extracts cooled at 0° overnight, yielding from Me an acid, m. p. 108° (0·05 g.) (Found: equiv., 98), and, from Pr, azelaic acid (0·04 g.), m. p. 102° (from benzene) (Found: equiv., 93. Calc. for $C_9H_{16}O_4$: equiv., 94). The light petroleum mother-liquors afforded, on evaporation, sharp-smelling, lemon-yellow oils [from Me, 0·40 g., equiv., 176; alkaline hydrolysis gave decanoic acid, m. p. 31·5° (lit., 31·5°) (Found: equiv., 174. Calc. for $C_{10}H_{20}O_2$: equiv., 172); from Pr, equiv., 176 (hydrolysis gave an acid of equiv. wt., 179].

The acids insoluble in hot light petroleum were treated with absolute alcohol, concentrated, and cooled to 0°. The acids from Me yielded a trace of solid, m. p. 58—61° (Found: equiv., 300). The acids soluble in light petroleum, recovered and extracted with warm *cyclo*hexane, formed pasty waxes: from Me, nonanoic acid (0·05 g.), m. p. 10—12° (Found: equiv. 159.

Calc. for $C_9H_{18}O_2$: equiv., 158); from Pr, an acid (0·12 g.), m. p. 23° (Found: equiv., 189). Materials insoluble in *cyclo*hexane were similar pasty waxes. This Me wax (0·07 g.) (Found: equiv., 147) was dissolved in hot alcohol and diluted with water until a faint emulsion was obtained: cooling to 0° afforded a flocculent colourless solid (0·03 g.) (Found: equiv., 200), and a brown wax (0·03 g.), m. p. 30° (Found: equiv., 170. Calc. for decanoic acid, $C_{19}H_{20}O_2$: equiv., 172). The last wax (from Pr) (0·08 g.) yielded from chloroform–light petroleum at 0° a lemon-yellow solid (0·05 g.) (Found: equiv., 120).

(c) *Resolution of the neutral substances.* The neutral oils (7·6 g. from Me; 11·6 g. from Pr) strongly reduced Fehling's solution. Solutions in alcohol (7 pts. by wt.) at 0° were treated with water to a faint permanent cloudiness. After 120 hours at 0°, the precipitates were collected [from Me, very little; from Pr, 1·1 g. of a yellowish oil (room-temp.) (V, below]. The residual materials recovered by evaporation and ether-extraction gave no precipitates from acetone, chloroform, or light petroleum at 0°. They gave on analysis: sap. val., Me 284, Pr 261; I.V., Me 34·4, Pr 41·6; active O, Me 0·808, Pr, 0·465%; *M* (Rast), Me 301, Pr 364.

Further samples of neutral oils were hydrolysed for 1 hour with 50% alcohol containing 10% of potassium hydroxide, yielding dihydroxystearic acid [m. p. (lit.) 132°]: from Me (5·4 g.), 0·20 g., m. p. 130° (Found: equiv., 314); from Pr (7·8 g.), 0·30 g. (Found: equiv., 316·5). The ether-soluble filtrates from these acids yielded oils which were thrice extracted with light petroleum; these solutions at 0° gave, from Pr, a precipitate (0·03 g.), m. p. 95° (Found: equiv., 294). In this experiment, Me gave elaidic acid epoxide, m. p. 53° (0·30 g.) (Found: equiv., 296. Calc. for $C_{18}H_{34}O_3$: equiv., 298) [hydrolysed to dihydroxystearic acid, m. p. 128° (Found: equiv., 320)]. The light petroleum filtrate from Me yielded a yellow oil which in aqueous alcohol deposited a small amount of elaidic acid, m. p. 43° (Found: equiv., 283. Calc. for $C_{18}H_{34}O_2$: equiv., 282).

Some heterogeneous resinous mixtures were left from the light petroleum extractions, in the case of Me sufficient for further resolution. A white solid (0·03 g.), washed out with light petroleum and recrystallised from aqueous alcohol, was crude dihydroxystearic acid, m. p. 125° (Found: equiv., 310). The residual resin gave from benzene a precipitate, m. p. 105° (Found: equiv., 320); the resin reduced Fehling's solution and had equiv. 295, I.V. 16·6; it was a C_{18} ketonic product.

Examination of the original neutral oils by mild hydrolytic distillation. The oils (*ca.* 5 g.) were refluxed with 0·1N-sodium hydroxide (100 ml.) for 2 hours and the small yields of volatile oils were trapped in a sealed-in U tube. Both were of sharp odour and zero titre, and strongly reduced Fehling's solution {from 3·49 g. of Me, 0·0605 g.; from 7·80 g. of Pr, 0·124 g. [Found: I.V., 29·5; *M* (Rast), 240; CO (ketone), 9·3%]}. The non-volatile materials from Me and Pr had, respectively: *M* (Rast), 301, 364; active O, 0·56, 0·57%; sap. val., 252, 236; I.V., 26·1, 31·8; CO, 2·8, 2·6%.

Infra-red Analysis.—The following materials were examined by means of a recording double-beam infra-red spectrometer with a rock-salt prism: (I) The neutral oil isolated from the oxidation of methyl elaidate at 98° after removal of the small volatile fraction by the Ellis U-tube method for ketones. (II) As (I) but before removal of the volatile fraction. (III) The neutral oil from oxidation of *n*-propyl elaidate at 120°, after removal of the small volatile fraction as above. (IV) As (III), but before removal of the volatile fraction. (V) Precipitate from cold alcoholic treatment of neutral oil from oxidised *n*-propyl elaidate. (VI) The final oil obtained from the attempt at low-temperature separation of elaidic acid oxidised at 98°. A constant thickness of liquid was used.

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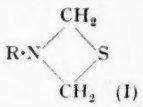
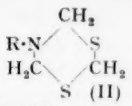
28. *The Action of Hydrogen Sulphide on Certain Methyleneimines. Part II.**

By Eric R. Braithwaite and John Graymore.

The reaction of hydrogen sulphide with *N*-methylene-*cyclo*hexylamine and -benzylamine in the presence of formaldehyde has been re-examined. The experiments have been extended to *p*-methoxy- and 2 : 4 : 6-trimethyl-*N*-methylenebenzylamine.

It has been shown (Part I *) that reaction of hydrogen sulphide and formaldehyde with *N*-methylene-*cyclo*hexylamine or -benzylamine leads to dissimilar products formulated as (I) and (II) or (III) respectively. This was thought to be due to the methyleneimines having monomeric and dimeric structures respectively, but their infra-red absorption spectra show that in fact neither is monomeric. This discrepancy has now been shown to be largely apparent, for under somewhat different conditions *N*-methylene*cyclo*hexylamine affords a product of type (III), and *N*-methylenebenzylamine yields a compound of the type (I) though a benzyl analogue of (II) has so far proved unobtainable. Moreover, in the cases of *p*-methoxy- and 2 : 4 : 6-trimethyl-*N*-methylenebenzylamine compounds of all three types (I), (II), and (III) have been obtained.


(I)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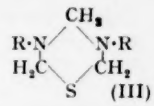
(III)

(R = C_6H_{11} or CH_2Ph)

Preliminary experiments revealed, first, that variation in the volume of formaldehyde used had no effect on the type of compound formed, provided that the weight of hydrogen sulphide was constant. Secondly, the passage of hydrogen sulphide at temperatures above normal quickly gave rise to the formation of intractable complexes of low nitrogen content. Except in the case of *N*-methylenebenzylamine, it was convenient to carry out the experiments on aqueous-ethanolic formaldehyde solutions of the methyleneimines as the latter were not readily precipitated from this medium by water.

The previous failure to obtain 3 : 5-di*cyclo*hexyltetrahydro-1-thia-3 : 5-diazine (III; R = C_6H_{11}) was thought to have one of two causes: either the thiadiazine was readily converted into 3-*cyclo*hexyl-1-thia-3-azetidine or 5-*cyclo*hexyl-5 : 6-dihydro-1 : 3-dithia-5-azine; or excess of hydrogen sulphide favoured the formation of the monomeric form of methylene*cyclo*hexylamine, which then condensed with formaldehyde and hydrogen sulphide to give (I) and/or (II) (R = C_6H_{11}). With the latter possibility in mind, attempts were made to produce 3 : 5-di*cyclo*hexyltetrahydro-1-thia-3 : 5-diazine by using the calculated quantity of hydrogen sulphide, but the product was mainly 3-*cyclo*hexyl-1-thia-3-azetidine, with a small quantity of 5-*cyclo*hexyl-5 : 6-dihydro-1 : 3-dithia-5-azine. Experiments in which various weights of hydrogen sulphide were used have finally shown that, by adding it to a mixture of *N*-methylene*cyclo*hexylamine and formaldehyde, approx. 60% of the theoretical amount of hydrogen sulphide dissolved in formaldehyde solution, a solution can be obtained which remains clear after 24 hours; from this 3 : 5-di*cyclo*hexyltetrahydro-1-thia-3 : 5-diazine was readily obtained on the addition of water.

A similar result was obtained with *N*-methylenebenzylamine. In contrast, *p*-methoxy- and 2 : 4 : 6-trimethyl-*N*-methylenebenzylamine afforded chiefly a product of type (III) but each gave also a little (I). *N*-Methylene-*cyclo*hexylamine and -benzylamine gave high yields of the corresponding thiazetidine (I) when treated in the presence of formaldehyde with 1—2 mols. of hydrogen sulphide. The other methyleneimines gave mixtures of types (I) and (III) from which type (I) was obtained in good yield.

It is noteworthy that, save with *N*-methylene*cyclo*hexylamine from which a small amount of 5-*cyclo*hexyl-5 : 6-dihydro-1 : 3-dithia-5-azine was isolated, compounds of type (II) have not been detected, despite the fact that both *p*-methoxy- and 2 : 4 : 6-tri-

* Part I, *J.*, 1950, 208.

methyl-*N*-methylenebenzylamine yield compounds of type (II) under slightly different conditions. A crystalline thiosulphate was obtained from *p*-methoxybenzylamine. It is hoped to examine the reaction of other aldehydes towards the methyleneimines in the presence of hydrogen sulphide.

Experimental

p-*Methoxy*-N-*methylenebenzylamine.*—*p*-Methoxybenzylamine (5·5 c.c.) was dissolved in ethanol, and 40% formaldehyde solution (3·5 c.c.) added. The mixture, which became hot, was cooled. After several hours, the precipitated solid was removed and on crystallizing from ethanol gave p-*methoxy*-N-*methylenebenzylamine* as steel-grey needles, m. p. 115—116° [Found: N, 9·4%; *M* (Rast), 151. $C_9H_{11}ON$ requires N, 9·4%; *M*, 149]. *N*-Methylene-*cyclo*hexylamine and -benzylamine were prepared by the same method. 2 : 4 : 6-Trimethyl-*N*-methylenebenzylamine was prepared by Fuson and Denton's method (*J. Amer. Chem. Soc.*, 1941, **63**, 654).

Tetrahydro-1-*thia*-3 : 5-*diazines.*—The preparation of 3 : 5-*di*cyclo*hexyltetrahydro*-1-*thia*-3 : 5-*diazine* illustrates the general procedure used for the preparation of compounds of type (III). To a solution of *N*-methylene*cyclo*hexylamine (1 g.) in ethanol (25 c.c.) was added 40% formaldehyde solution (10 c.c.). The mixture was cooled to <20°. Any solid separating was removed. Meanwhile, hydrogen sulphide was passed with cooling through 40% formaldehyde solution (10 c.c.) until the increase in weight was 0·09 g. (0·60 mol.). The solutions were mixed and kept overnight at 0°, remaining clear. Gradual addition of water then precipitated the thiadiazine as needles. In later experiments, it was found advisable to seed the liquor after addition of a little water, to avoid precipitation as an oil. Recrystallization from ethanol–water gave the pure compound in needles, m. p. 51° (Found: C, 67·2; H, 10·4; S, 11·7. $C_{15}H_{28}N_2S$ requires C, 67·2; H, 10·4; S, 11·9%).

3 : 5-*Dibenzyltetrahydro*-1-*thia*-3 : 5-*diazine.* Condensation was effected by the general method but without the preliminary addition of formaldehyde, as this tended to precipitate the methyleneimine. 0·7 Mol. of hydrogen sulphide was used and the thiadiazine separated overnight. A further quantity was obtained on addition of a small quantity of water to the filtrate. Recrystallized from ethanol it was obtained as needles, m. p. 92—93° (Found: C, 71·6; H, 7·3; N, 10·1; S, 10·6. Calc. for $C_{17}H_{20}N_2S$: C, 71·8; H, 7·0; N, 9·8; S, 11·3%).

3 : 5-*Di*-p-*methoxybenzyltetrahydro*-1-*thia*-3 : 5-*diazine.* On use of the general method, crystals separated after 3 hours. Collection after 24 hours and repeated recrystallization from ethanol gave needles, m. p. 162° (Found: C, 66·3; H, 7·0; N, 8·0, 8·1; S, 9·3, 9·5. $C_{19}H_{24}O_2N_2S$ requires C, 66·3; H, 7·0; N, 8·1; S, 9·3%). The *thiadiazine* was also obtained by passing hydrogen sulphide through an ethanolic solution of the methyleneimine admixed with formaldehyde. As soon as separation commenced, passage of hydrogen sulphide was stopped and the flocculent precipitate removed. Recrystallized from ethanol, it gave the thiadiazine in needles, m. p. 162°.

3 : 5-*Di*-(2 : 4 : 6-*trimethylbenzyl*)*tetrahydro*-1-*thia*-3 : 5-*diazine.* 2 : 4 : 6-Trimethyl-*N*-methylenebenzylamine was dissolved in boiling ethanol (60 c.c.) and the general procedure followed. After 24 hours the precipitated *thiadiazine* was recrystallized from ethanol (needles: m. p. 158—159°) (Found: C, 74·6; H, 8·7; N, 7·4; S, 8·5. $C_{23}H_{32}N_2S$ requires C, 75·0; H, 8·7; N, 7·6; S, 8·7%). It dissolves in chloroform, acetone, or boiling ethanol or methanol.

Preparation of 1-*Thia*-3-*azetidines* (I).—*General method.* The methyleneimine (1 g.) was dissolved in boiling ethanol (25 c.c.), 40% formaldehyde solution (10 c.c.) was added, and the mixture cooled. Any solid remaining was removed. Hydrogen sulphide was passed into a further quantity of 40% formaldehyde solution (10 c.c.) until the increase in weight was 0·3 g. This solution was then added to the methyleneimine mixture. Separation of crystals began almost immediately but the mixture was left overnight at 0° to complete the separation. Recrystallization was usually from alcohol or from acetone.

3-*cyclo*Hexyl-1-thia-3-azetidine crystallized from acetone in needles, m. p. and mixed m. p. 118—119° (yield, 0·7 g.).

3-*Benzyl*-1-*thia*-3-*azetidine* (yield 0·6 g.), crystallized from ethanol, had m. p. 116° (0·5 g.) (Found: C, 65·1; H, 7·0; N, 8·2; S, 18·9. $C_9H_{11}NS$ requires C, 65·6; H, 6·7; N, 8·5; S, 19·3%).

3-p-*Methoxybenzyl*-1-*thia*-3-*azetidine* was obtained in needles, m. p. 144—145° (Found: N, 7·45; S, 16·2. $C_{10}H_{13}ONS$ requires N, 7·2; S, 16·4%), after fractional crystallization from ethanol to remove the thiadiazine.

3-(2 : 4 : 6-*Trimethylbenzyl*)-1-*thia*-3-*azetidine.* 2 : 4 : 6-Trimethyl-*N*-methylenebenzylamine

(1 g.) needed 60 c.c. of boiling ethanol for dissolution. The azetidine, m. p. 145—161°, was removed and a further quantity obtained on addition of water to the filtrate. Recrystallized from hot methanol–acetone, this *thia-azetidine* was obtained as needles, m. p. 182° (Found: N, 6·9; S, 15·4. $C_{12}H_{17}NS$ requires N, 6·7; S, 15·4%). A small quantity of the corresponding thiadiazine was obtained from the mother-liquor.

5 : 6-*Dihydro*-5-(2 : 4 : 6-*trimethylbenzyl*)-1 : 3-*dithia*-5-*azine*.—2 : 4 : 6-Trimethyl-*N*-methylenebenzylamine (5 g.) was dissolved in the min. of cold dioxan and formaldehyde (40% solution) was added until a faint opalescence was evident. The solution was saturated with hydrogen sulphide with cooling and then kept overnight. Addition of water precipitated a sticky oil from which 5 : 6-*dihydro*-5-(2 : 4 : 6-*trimethylbenzyl*)-1 : 3-*dithia*-5-*azine* was obtained on extraction with ethanol; it had m. p. 102° (Found: C, 61·5; H, 7·7; S, 25·2, 25·5; N, 5·4, 5·3. $C_{13}H_{19}NS_2$ requires C, 61·5; H, 7·5; S, 25·3; N, 5·5%). This compound was similarly obtained when hot ethanol replaced dioxan.

5 : 6-*Dihydro*-5-p-*methoxybenzyl*-1 : 3-*dithia*-5-*azine*.—40% Formaldehyde solution (10 c.c.) was saturated with hydrogen sulphide at room temperature and added to *p*-methoxy-*N*-methylenebenzylamine (1 g.) in ethanol (25 c.c.) containing 40% formaldehyde solution (10 c.c.). Hydrogen sulphide was then passed in for 20 minutes and the solution set aside overnight. Water was then added, precipitating a sticky solid. On extraction with ethanol, the solid remaining after evaporation recrystallized from aqueous alcohol as needles of the 5 : 6-*dihydrodithiazine*, m. p. 53° (Found: N, 6·0; S, 26·5. $C_{11}H_{15}ONS_2$ requires N, 5·8; S, 26·5%).

p-*Methoxybenzylamine Thiosulphate*.—*p*-Methoxybenzylamine (1 g.) was dissolved in ethanol (10 c.c.) and the solution saturated with hydrogen sulphide. Air was passed through the mixture. p-*Methoxybenzylamine thiosulphate* separated. Recrystallized from ethanol it had m. p. 181° (decomp.). It was soluble in water and gave the usual reactions for thiosulphates [Found: S, 16·4. $(C_8H_{11}ON)_2,H_2S_2O_3$ requires S, 16·4%].

Microanalyses were by Weiler and Strauss. The authors express their gratitude to Mr. C. S. Waight of British Rubber Producers' Research Association for his assistance in connection with absorption spectra.

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29. *The Structure of Native Poly-D-glutamic Acid. Part II.* Synthesis of α-Poly-L-glutamic Acid Hydrazide and the Curtius Degradation thereof.*

By J. KOVÁCS, V. BRUCKNER, and K. KOVÁCS.

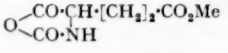
Methyl α-poly-L-glutamate was converted into the polyhydrazide, which was degraded by the Curtius method. Hydrolysis then gave αγ-diaminobutyric acid. This corroborates the previous conclusion (Part I*) that in native poly-D-glutamic acid the glutamyl units are, predominantly at least, in bonds other than α, since the analogous degradation and acid hydrolysis of the polyhydrazide prepared from native poly-D-glutamic acid affords no detectable quantity of αγ-diaminobutyric acid.

IT was reported (Kovács and Bruckner, *Research*, 1952, **5**, 194; Part I*) that poly-D-glutamic acid (molecular weight 6400) secreted by *B. subtilis* (Iványovics and Bruckner, *Naturwiss.*, 1937, **25**, 250; *Z. Immunforsch.*, 1937, **90**, 304; **91**, 175; Bruckner, Iványovics, and Kovács Oskolás, *Magyar Chem. Fol.*, 1939, **45**, 131; *Chem. Abs.*, 1940, **34**, 3766; Bovarnick, *J. Biol. Chem.*, 1942, **145**, 415) yields, on Curtius degradation of its polyhydrazide and subsequent hydrolysis, β-formylpropionic acid. This suggested the predominance of γ-peptide bonds (I), since αγ-diaminobutyric acid could not be isolated from the hydrolysate.

According to Hanby and Rydon (*Biochem. J.*, 1946, **40**, 297), poly-D-glutamic acid of lower molecular weight (*e.g.*, 6400)—resulting from partial hydrolysis of the original polymeric material of *B. anthracis* capsules during isolation—did not contain γ-glutamyl bonds. This would seem to be inconsistent with above statements, since the identity of the poly-D-glutamic acids of *B. subtilis* and *B. anthracis* of lower molecular weight (*e.g.*, 6400) appears to be established (Iványovics and Bruckner, *loc. cit.*).

* Part I, *J.*, 1952, 4255.

$$\cdots NH\cdot CH(CO_2H)\cdot[CH_2]_2\cdot CO\cdot NH\cdot CH(CO_2H)\cdot[CH_2]_2\cdot CO\cdots \quad (I)$$



$$\cdots NH\cdot CH(CH_2\cdot COR)\cdot CO\cdot NH\cdot CH(CH_2\cdot COR)\cdot CO\cdots$$

(II) (III; R = OMe) (IV; R = $NH\cdot NH_2$)

We now have investigated the analogous degradation of methyl α-poly-L-glutamate (III). This was prepared from 4-2′-carbomethoxyethyloxazolid-2 : 5-dione (II) by Hanby, Waley, and Watson (*J.*, 1950, 3239), using pyridine, and by Coleman (*J.*, 1950, 2294) who used dry pyridine, dioxan, ethyl acetate, or chloroform in the presence of the sodium salt of phenylalanine as initiator. Following the same route, except that water was preferred as initiator, we obtained a readily filtrable, colourless methyl α-poly-L-glutamate in almost quantitative yield.

The polyester readily formed a polyhydrazide (IV), with about 75% of the theoretical nitrogen content. It appears that the polyhydrazide undergoes partial hydrolysis of the hydrazide groups during its isolation. (The biuret reaction of this product is positive and is accompanied by slight reduction of the reagent.) In dilute alkaline solution the optical rotation shows the rapid decrease characteristic of α-polypeptides (Dakin, *J. Biol. Chem.*, 1912, **13**, 357; Levene and Bass, *ibid.*, 1929, **82**, 171; Levene, Bass, and Steiger, *ibid.*, p. 167; Dakin and Dudley, *ibid.*, 1913, **15**, 263; Bovarnick and Clarke, *J. Amer. Chem. Soc.*, 1938, **60**, 2426).

Curtius degradation of the polyhydrazide and subsequent acid hydrolysis afforded αγ-diaminobutyric acid, isolated as diflavianate and also as dipicrate. The assay gave positive results even when no more polyhydrazide was degraded (under exactly the same conditions) than the quantity of native poly-D-glutamic acid polyhydrazide (80—100 mg.) used in our former degradations. This further supports our opinion (Part I) that even *B. subtilis* poly-D-glutamic acids of low molecular weight cannot contain α-glutamyl bonds in appreciable proportion.

The yield of the αγ-diaminobutyric acid obtained as diflavianate from the hydrolysate was only 38·4%, being decreased by the following factors: (*a*) the polyhydrazide used as starting material was only about 75% pure (see above); (*b*) precipitation of the polyhydrazide starts before all hydrazide groups have reacted. For these reasons, no doubt, glutamic acid was always found in the hydrolysate.

Experimental

α-Methyl L-glutamate hydrochloride was prepared by a modification of Coleman's method (*loc cit.*): Finely powdered L-glutamic acid hydrochloride (15 g.) was shaken with anhydrous methanol (60 ml.) containing hydrogen chloride (0·8 g.) for 30 min. The solution, filtered from a trace of undissolved material, was quickly evaporated under reduced pressure at 40°. The solid residue was redissolved in hot dry methanol (16 ml.), mixed with dry ether (75 ml.), and set aside in the ice box; colourless prisms were formed, m. p. 154° (11·2 g.). With large quantities the yield was lower. Purification of large quantities of the crude material is preferably done by suspension in dry acetone, washing on the filter with the same solvent, and suction until dry.

4-2′-Carbomethoxyethyloxazolid-2 : 5-dione (II) was prepared by slight modification of Coleman's method (*loc. cit.*): γ-Methyl L-glutamate hydrochloride (100 g.), suspended in anhydrous dioxan (500 ml.), was saturated under vigorous stirring with carbonyl chloride (5 hours) at 40°. After most of the hydrochloride had dissolved, the mixture was filtered and evaporated under reduced pressure at 50°. The oily residue crystallized from anhydrous chloroform (100 ml.) on addition of 1 ml. of light petroleum, forming colourless crystals (45 g.), m. p. 99° (cf. Hanby, Waley, and Watson, *loc. cit.*; Coleman, *loc. cit.*).

Methyl α-Poly-L-glutamate (III).—The dione (II) is readily polymerised in moist dioxan or ethyl acetate. The following method was satisfactory: To (II) (33 g.) in anhydrous ethyl acetate (200 ml.) were added 5 drops of water; evolution of carbon dioxide set in and lasted for about 4 hours. After 2 days, the colourless solid polyester was collected, washed on the filter with hot water until the filtrate no longer gave the biuret reaction, and dried at 80°/1 mm. over P_2O_5 (yield 25 g.) [Found: N, 9·8; OMe, 20·7. Calc. for $(C_6H_9O_3N)_n$: N, 9·8; OMe, 21·7%].

(The water-soluble material was probably low polymers.) Similar treatment of (II) (55 g.) in dioxan (200 ml.) afforded polymer (40 g.) with a slight yellow tinge.

α-Poly-L-glutamic Acid Hydrazide (IV).—Finely powdered polyester was ground with 10 times its weight of anhydrous hydrazine and almost complelety dissolved on gentle boiling. The solution was cooled, centrifuged, and evaporated at 0·001 mm., and the residue ground with water and freeze-dried. Drying at 100°/1 mm. (P_2O_5) then gave the *hydrazide* as an almost colourless amorphous powder in nearly quantitative yield [Found: OMe, 0·1—0·5; N, 24·1—25·7. $(C_5H_9O_2N_3)_n$ requires N, 29·35%]. The product is readily soluble in dilute hydrochloric acid, and slightly soluble in dilute alkali. From dilute acid solutions flavianic acid precipitates the practically insoluble polyflavianate. When the polyhydrazide was dissolved in the minimum of N-hydrochloric acid, and the solution evaporated *in vacuo*, it afforded a polyhydrochloride readily soluble in water. This procedure, however, caused perceptible hydrolysis of the hydrazide groups, as indicated by the distinct increase of the solubility in N-alkalis.

Optical rotation. Polyhydrazide (0·504 g.) was dissolved in N-hydrochloric acid (2·6 ml.), the solution evaporated under diminished pressure, and the residue dissolved in water (2 ml.) and N-sodium hydroxide (13 ml.). The initial rotation, α_D −1·20° (l = 1), gradually decreased during 10 days to α_D −0·20°. In order to confirm that this decrease was due to partial racemization and not to hydrolytic decomposition, we ran a control as follows. The 10-days old alkaline solution was acidified (5 ml. of concentrated hydrochloric acid) and then evaporated under reduced pressure. The residue was redissolved in concentrated hydrochloric acid (6 ml.) and refluxed for 6 hours, the hydrochloric acid removed by evaporation, and the residue dissolved in water (8·5 ml.). After addition of a minute quantity of charcoal the solution was filtered; it had α_D +0·10° (l = 1) whereas a solution of 0·64 g. of L-glutamic acid hydrochloride (equiv. to 0·504 g. of polyhydrazide), 0·35 g. of hydrazine dihydrochloride, and 0·76 g. of sodium chloride in 8·5 ml. of water had α_D +1·49° (l = 1). This is considered to prove that the decrease of the rotation of the polyhydrazide in alkaline solution results from racemization.

Degradation of α-L-Polyglutamic Acid Hydrazide.—(*a*) A solution of polyhydrazide (180 mg.) in N-hydrochloric acid (1·4 ml.) was evaporated under reduced pressure, and the residue dissolved in water (2 ml.). With cooling and stirring, 4·1% sodium nitrite solution (1·94 ml.) was added (10 min.). The gummy precipitate and the turbid solution were warmed over a micro-burner until foaming ceased and the precipitate coagulated (1—2 min.), concentrated hydrochloric acid (20 ml.) was added, and on further warming (10 min.) the precipitate completely dissolved. The solution was evaporated under reduced pressure, the residue redissolved in concentrated hydrochloric acid (10 ml.), and the whole refluxed for 15 hours, and then evaporated to dryness. The residue was dissolved in water (0·6 ml.), saturated aqueous picric acid (10 ml.) added, and the solid (a few mg.) collected next day and washed repeatedly with water (total, 4 ml.). The m. p. (185°) rose after one recrystallization from water (2 ml.) to 188—189° undepressed on admixture with L-αγ-diaminobutyric acid dipicrate, m. p. 187—189° (Found: C, 33·7; H, 3·1. Calc. for $C_{16}H_{16}O_8N_8$: C, 33·3; H, 2·8%). In another experiment the polyhydrazide (77 mg.) was decomposed under the conditions employed in the degradation of native D-polyglutamic acid (83 mg.) (Kovács and Bruckner, *loc. cit.*), and 2 mg. of diaminobutyric acid dipicrate were isolated.

(*b*) To a solution of polyhydrazide (250 mg.) in 0·3N-hydrochloric acid (12 ml.), with stirring and cooling, 5·2% sodium nitrite solution (2·5 ml.) was added dropwise. The mixture was worked up as under (*a*) except that hydrolysis was for only 4 hours. The residue obtained on evaporation was redissolved in hot water (2·5 mm.) in which flavianic acid (1 g.) was then dissolved. On cooling, the solution set to a mass of crystals. The product was collected, and washed with cold water, methanol, and then ether, a yield of 496 mg. (38·4%) of dry flavianate being obtained; m. p., after one recrystallization from water, 239°, as reported for L-αγ-diaminobutyric acid diflavianate (Found: C, 38·2; H, 3·2; N, 11·0. Calc. for $C_{24}H_{22}O_{18}N_6S_2$: C, 38·5; H, 3·0; N, 11·25%). In another experiment the degradation of the polyhydrazide (100 mg.) and the assay of αγ-diaminobutyric acid were carried out under the conditions of our previous degradation of native D-polyglutamic acid (195 mg.) in which no diaminobutyric acid diflavianate could be obtained (from 97·5 mg. of polyhydrazide), but in the present experiment 26·2 mg. of diflavianate were obtained.

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30. *The Structure of Native Poly-D-glutamic Acid. Part III.**

By V. Bruckner, J. Kovács, and H. Nagy.

Poly-D-glutamic acid, secreted by *B. subtilis* in the culture medium, was isolated as the acid sodium salt and thence converted directly into the polymethyl ester. Conversion of this into the polyamide followed by Hofmann degradation and acid hydrolysis, gave β-formylpropionic acid but no detectable quantities of αγ-diaminobutyric acid. The quantity of β-formylpropionic acid isolated as its *p*-nitrophenylhydrazone suggests that probably only γ-glutamyl bonds are present in the polyacid, since no evidence has been found for α-glutamyl bonds.

In Part I (*J.*, 1952, **4255**; see also Kovács and Bruckner, *Research*, 1952, **5**, 194) it was reported that the poly-D-glutamic acid secreted in the culture medium by *B. subtilis*, and of molecular weight *ca.* 6400, contains mainly γ-glutamyl bonds. This conclusion was based on the absence of αγ-diaminobutyric acid, which could readily have been identified (Kovács, Bruckner, and Kovács, Part II *), from the products of hydrolysis of the poly-glutamylhydrazine obtained from the acid *via* the methyl ester. Since, however, the yield of β-formylpropionic acid, isolated as its *p*-nitrophenylhydrazone from the hydrolysate was only 14·5% of that to be expected from a pure hydrazide, we sought to obtain a better yield by degradation of the polyacid amide by Hofmann's method.

For this purpose we used poly-D-glutamic acid produced by a strain of *B. subtilis* apparently identical with that used by Bovarnick (*J. Biol. Chem.*, 1942, **145**, 415). In view of Hanby and Rydon's suggestion (*Biochem. J.*, 1946, **40**, 297) that the acid used by Ivánovics and Bruckner (*Z. Immunforsch.*, 1937, **90**, 304; **91**, 175; *Naturwiss.*, 1937, **25**, 250) had been partly degraded by too long contact with acid, we took precautions to minimise this. From the copper salt of the acid, we prepared the sodium salt, and thence the polymethyl ester (I). This was not quite homogeneous and was divided into two fractions, one containing a trace of ash, and the other ash-free. The latter had a molecular weight of *ca.* 10,000, as calculated from its amino-nitrogen content (0·14%), corresponding to 9000 for the free poly-D-glutamic acid. Although this is higher than the values, 6400—7100, found for preparations isolated by Ivánovics and Bruckner's method (*loc. cit.*), it is much lower than the maximum values obtained by Hanby and Rydon (*loc. cit.*) for the acid obtained from the capsules of *B. anthracis*, *viz.*, 45,300. The methoxyl contents of the two fractions indicated 94 and 89% esterification of the carboxyl groups.

Both polymethyl ester fractions were readily converted into the amide (II) by liquid ammonia in a sealed tube at 25—30°, but the nitrogen contents of the amide were slightly low (20·6 and 21·5. Calc.: 21·8%). Fraenkel-Conrat, Olcott, and Cooper (*J. Amer. Chem. Soc.*, 1945, **67**, 950) prepared the polyamide by a similar method and concluded, from analyses for total and amido-nitrogen, that only 80% of the ester groups had undergone amidation, but in our opinion such analyses do not give a reliable measure of the degree of amidation since some of the original carboxyl groups escape esterification and are converted into ammonium salts. As calculated from our esterification values (above), amidation appears to give polyamide of *ca.* 90% purity.

$$\underset{\text{(I; R = CO}_2\text{Me)}}{\text{NH}_2\cdot\text{CHR}\cdot[\text{CH}_2]_2\cdot\text{CO}\cdot[\text{NH}\cdot\text{CHR}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}]_n\cdot\text{NH}\cdot\text{CHR}\cdot[\text{CH}_2]_2\cdot\text{R}} \quad \underset{\text{(II; R = CO}\cdot\text{NH}_2\text{)}}{} \quad \underset{\text{(III; R = NH}_2\text{)}}{}$$

$$\text{(III)} \longrightarrow (n+1)\underset{\text{(IV)}}{\text{OHC}\cdot[\text{CH}_2]_2\cdot\text{CO}_2\text{H}} + \underset{\text{(V)}}{\text{OHC}\cdot[\text{CH}_2]_2\cdot\text{NH}_2}$$

The polyamide was degraded by Hofmann's method, the resulting solution hydrolysed by hydrochloric acid, and β-formylpropionic acid (IV) precipitated as its *p*-nitrophenylhydrazone. αγ-Diaminobutyric acid could not be detected even by flavianic acid. No

* Part II, preceding paper.

reaction could be obtained for β-aminopropaldehyde (V) which would be formed from the terminal unit in (III) on hydrolysis, but as this substance is rather unstable and would be formed in only very small amount, this failure is not regarded as significant.

Best yields of β-formylpropionic acid were obtained by use of the theoretical quantity of sodium hypochlorite and then brief hydrolysis with 10% hydrochloric acid: 50 mg. of polyamide gave 38 mg. (41%) of β-formylpropionic acid *p*-nitrophenylhydrazone. However, in control experiments with β-formylpropionic acid only 47—54% yields of the *p*-nitrophenylhydrazone were obtained, so, as our polyglutamide was only 90% pure, we regard the above results as indicating the presence in poly-D-glutamic acid of γ-glutamyl bonds almost exclusively, with little if any α-glutamyl bonds.

The degradation product (III) appears to undergo slight hydrolysis in the alkaline hypochlorite solution since towards the end of the reaction ammonia can be smelled. This fact would account for at least part of the slight deficiency of the *p*-nitrophenylhydrazone in the actual as compared with the control experiments.

Experimental

Methyl Poly-D-glutamate.—*B. subtilis* strain No 16, of the Institute of Medical Chemistry of the University of Budapest, was used, and was found to be identical with strain No. 712 of the Department of Agriculture, U.S.A., used by Bovarnick (*loc. cit.*). The medium was worked up according to her method, and the polypeptide precipitated as its copper salt. This was dissolved in 1·5N-hydrochloric acid, and the solution dialysed first against a citrate buffer (0·5M, pH 5·0), and then, after removal of copper ions, against distilled water and freeze-dried until the volume was about 30 ml. Methanol–ether (100 + 20 ml.) precipitated the acid sodium salt of D-polyglutamic acid. The supernatant liquid was removed, and the sticky precipitate washed in the centrifuge four times with methanol, and dried ($CaCl_2$) in a vacuum-desiccator. The product was then dissolved in a small quantity of water, and the solution evaporated by freeze-drying. The residue was dried at 60°/0·001 mm (P_2O_5) to an almost colourless powder (5 g.). A suspension of this substance (4 g.) in absolute methanol (100 ml.) was mixed with 2 ml. of acetyl chloride. On shaking, within a few minutes, almost complete dissolution occurred with slight evolution of heat. The solution was kept at room temperature for 12 days with exclusion of atmospheric moisture, after which any precipitated material (mostly inorganic) was removed on the centrifuge. Absolute ether (35 ml.) precipitated from the remaining solution a copious solid (no longer sticky) which was isolated by centrifuge, and washed with a small amount of absolute methanol. These washings and the original mother-liquor were mixed and retained (solution A), and the precipitate was further washed three times with 15 ml. of water on the centrifuge, the washings being collected (solution B). Only 0·2 g. remained undissolved.

(*a*) Mixture A was mixed with 2 vols. of absolute ether. A gum appeared on the sides of the flask; this was dissolved in 40 ml. of methanol, and reprecipitated by absolute ether. It was then freed from solvents on the centrifuge and washed three times with small amounts of water. The aqueous washings (C) were added to solution B. The water-insoluble polymethyl ester was dried *in vacuo* (P_2O_5), powdered, and again dried (P_2O_5) for 4 hours at 100°/1 mm. The resulting product (0·6 g.) was ash-free [Found: MeO, 20·3; total N, 9·5. Calc. for $(C_6H_9O_3N)_n$: MeO, 21·7; total N, 9·8%]. The amino-N was 0·14%.

(*b*) The combined liquors B and C were evaporated *in vacuo* at room temperature, and the residue washed three times on the centrifuge with water (3 × 5 ml.) and then dried in a vacuum-desiccator. The product was powdered, dissolved in warm methanol, and mixed with an equal volume of water, the solution freeze-dried, and the remaining product dried for 4 hours (P_2O_5) at 100°/1 mm., giving an almost colourless substance of loose, cottony appearance (0·9 g.) (Found: ash, 0·8; MeO, 19·3; total N, 9·7; amino-N, 0·17%). The last value indicates a molecular weight of 8240, corresponding to *M* 7430 for the free polyacid.

Poly-D-glutamic Acid Amide.—(*a*) The ash-free polyester (0·5 g.) was kept in liquid ammonia (distilled from sodium) (30 ml.) in a sealed tube at room temperature for 48 hours, the ammonia evaporated, and the residue dissolved in water. Some insoluble substance was removed by filtration, and the filtrate freeze-dried. The colourless, cottony residue (0·4 g.) was dried at 78°/0·001 mm. for 12 hours [Found: total N, 20·6; amido- + ammonium-N, 10·0; MeO, 0·3. Calc. for $(C_5H_8O_2N_2)_n$: total N, 21·8; amido-N, 10·9; MeO, 0·0%].

(*b*) The other polyester (*b*) (380 mg.) was similarly treated, but the final solid was washed

on the centrifuge three times with 3 ml. of cold water, then dried first by freeze-drying and later at 100°/1 mm. (P_2O_5) (15 hours); the yield was 185 mg. (Found: total N, 21·5; amido- + ammonium-N, 10·7; ash, 0·5; MeO, 0·2%).

Degradation of the Polyamide.—(*a*) Polyamide (*a*) (50 mg.) was dissolved at room temperature in 1·4% sodium hypochlorite solution (2·1 ml.); dissolution occurred within a few minutes save for a few flocks, and after 1 hour the smell of ammonia appeared. When the mixture was immersed for 10 minutes in a water-bath at 50°, the flocks disappeared. Then the mixture was cooled to room temperature, acidified with concentrated hydrochloric acid (10 ml.), and refluxed for 30 minutes. The solution was evaporated *in vacuo*, water added, and the solution evaporated to dryness. The remaining solid was mixed with 12 drops of a freshly prepared solution of *p*-nitrophenylhydrazine in N-hydrochloric acid, put for a few seconds into boiling water, and cooled again under the tap. The yellow crystalline solid was collected, washed on the filter with a total of 3 ml. of water, and dried *in vacuo* (P_2O_5); the yield was 32 mg. (*i.e.*, 38·4% of theory for a 90% pure polyamide); the m. p. was 170—172°, raised by one recrystallisation from water to 178°, undepressed by authentic β-formylpropionic acid *p*-nitrophenylhydrazone.

(*b*) Polyamide (*b*) (50 mg.) was similarly treated, the addition of hydrochloric acid being adjusted to give a 10% concentration in 5 ml. of solution, which was refluxed for 30 minutes and worked up as under (*a*); 38 mg. of *p*-nitrophenylhydrazone were obtained (*i.e.*, 45·6% on the basis of a 90% pure polyamide); m. p., etc., as in (*a*).

(*c*) Polyamide (*a*) (50 mg.) was degraded as under (*a*), and the alkaline mixture acidified and evaporated to dryness, the residue being redissolved in concentrated hydrochloric acid (10 ml.) and refluxed for 4 hours. After removal of the acid by distillation, the residue was again dissolved in water, but αγ-diaminobutyric acid could not be detected either as dipicrate (Kovács and Bruckner, *loc. cit.*) or even with flavianic acid.

Control Experiments.—(i) From 36 mg. of freshly prepared β-formylpropionic acid (the amount which would be expected to be formed on degradation from 50 mg. of 90% pure γ-polyglutamic amide), b. p. 132°/14 mm., in a series of experiments (precipitation by 12 drops of the usual reagent, filtration, repeated washings with a total of 3 ml. of water, and drying), the yield of *p*-nitrophenylhydrazone, m. p. 172—173°, was 71—77 mg. (85·3—92·5%). (ii) A solution of 36 mg. of freshly prepared β-formylpropionic acid in 5 ml. of 10% hydrochloric acid was refluxed for 30 minutes, and the solution worked up as for the hydrolysate in the degradation experiments; the yield of *p*-nitrophenylhydrazone, m. p. 172—173° was 39—45 mg. (46·6—53·8%). (iii) When 36 mg. of β-formylpropionic acid were kept in 1·5—2·1 ml. of 8·5% sodium hydroxide solution for 1 hour at room temperature, and 10 minutes at 50°, then treated with hydrochloric acid, as in the methods described earlier, and refluxed for 30 minutes, the residue obtained in the usual way no longer gave detectable quantities of the *p*-nitrophenylhydrazone. (iv) Since sodium hypochlorite degrades glutamic acid to β-formylpropionic acid (Langheld, *Ber.*, 1909, **42**, 2360), we ran controls in order to study the alkaline hydrolysis of poly-D-glutamic acid under the conditions of the Hofmann degradation of the polyamide. We found that in alkaline (8·5%) solutions of the polyacid the amino-N, 0·22, increased only to 0·29, showing that no appreciable hydrolysis occurs under the conditions of the Hofmann degradation.

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31. *The Polymerisation of α-Methylstyrene catalysed by Stannic Chloride in Ethyl Chloride Solution.*

By F. S. Dainton and R. H. Tomlinson.

An apparatus is described for the dilatometric measurement of the rate of polymerisation of α-methylstyrene by stannic chloride in carbon tetrachloride solution and for the quantitative separation of the dimer, trimer, tetramer, and pentamer from higher polymers produced. The infra-red absorption spectra and the chemical properties indicate that the polymers are saturated, and they are considered to possess a substituted phenylindane end group. Water is a co-catalyst, but the reaction rate is independent of the co-catalyst : catalyst concentration ratio when this quantity exceeds *ca.* 3. When D_2O is used as a co-catalyst the resultant polymer contains C–D linkages, and the initial reaction rate is lower than when H_2O is the co-catalyst; but the reaction then accelerates until it reaches the rate characteristic of the latter system. The rate of reaction is equal to $k_1[SnCl_4]^{3/2}[m_1]^y$, where y increases with m_1 from 1·2 towards 2, and $k_1 = k_1^\circ \exp(3{\cdot}5 \text{ kcal.}/\boldsymbol{R}T)$. The degree of polymerisation of the product is equal to $2 + k_2[m_1]$, where $k_2 = k_2^\circ \exp(4{\cdot}5 \text{ kcal.}/\boldsymbol{R}T)$. A reaction mechanism is proposed to account for these results, in which the initiation process is the abstraction of a proton by the monomer from the catalyst–co-catalyst complex. Growth of the polymer chain then follows by the usual carbonium-ion mechanism and the termination step is one of spontaneous proton release, which may be accompanied by cyclisation. It is concluded that $E_i = 1$ kcal., $E_t - E_p \doteqdot 4{\cdot}5$ kcal., and $A_p/A_t \doteqdot 1{\cdot}2 \times 10^{-3}$ l. mole^{-1}.

A study of the polymerisation of α-methylstyrene induced by traces of Friedel–Crafts catalysts was undertaken for several reasons. First, the resonance stabilisation of the monomer due to conjugation of the aromatic nucleus with the ethylenic double bond, and the steric strain in the polymer due to αα′-disubstitution, are both factors which make for a low heat of polymerisation, and hence, if the entropy of this polymerisation has its normal value ($\Delta S^\circ_{lsm} \sim -30$ cal./deg. mole), the ceiling temperature (cf. Dainton and Ivin, *Trans. Faraday Soc.*, 1950, **46**, 331) should also be low. Some support for this view is provided by the fact that α-methylstyrene cannot be polymerised above ~80°. Accepting the above value of ΔS°_{lsm}, we deduce that, if $Tc_{lsm} \sim 350°$ K, then $\Delta H_{lsm} < 10$ kcal. Jessup and Roberts (cited by Roberts, *J. Res. Nat. Bur. Stand.*, 1949, **44**, 221) have recently measured the heat of conversion of liquid monomer into various polymers of low molecular weight and has obtained values of 10 kcal. for an average degree of polymerisation of 7·6. α-Methylstyrene therefore seemed to be a suitable monomer for investigating propagation–depropagation equilibria in cationic polymerisation. Secondly, the results of the earlier workers indicated that low-molecular-weight products are formed at room temperature, and this condition is favourable to the application of infra-red spectroscopic methods for the detection of end-groups. Thirdly, according to Pepper's work (*Trans. Faraday Soc.*, 1949, **45**, 425), the reaction is sensitive to changes of dielectric constant of the medium and insensitive to moisture, and the molecular weight of the polymer can be determined by addition of bromine to the double bond at the end of each polymer chain. The results of our preliminary experiments were so different from those of previous workers that the original objects of the investigation were modified so as to become merely the exploration of the kinetics of the polymerisation in ethyl chloride solution of α-methylstyrene catalysed by stannic chloride, care being taken to handle all chemicals *in vacuo* with carefully controlled quantities of added water, to measure initial reaction rates dilatometrically, and to investigate both the molecular weight and the structure of the polymers formed.

Experimental

(a) *Materials.*—α-Methylstyrene, given by the Distillers Company Ltd., was stored over nitrogen. Before use it was degassed and distilled twice *in vacuo*, only the middle third fraction being kept each time. Ethyl chloride, supplied by B.D.H. Ltd., was dried [$Mg(ClO_4)_2$], out-

gassed by pumping and freezing, and distilled from the perchlorate at the temperature of solid carbon dioxide to a storage trap surrounded by liquid air. Only the first two-thirds of the distillate was retained. Stannic chloride was outgassed and distilled *in vacuo*, only the third quarter of the distillate being returned.

All chemicals were handled *in vacuo* throughout.

(b) *Dilatometers.*—These consisted of bulbs made from 8-mm. Pyrex tubing joined to precision capillary tubing of uniform cross-sectional area = 0·776 mm.^{2}. Within each dilatometer bulb was a magnetic stirrer made of iron wire sealed in glass tubing, which could be alternately raised and lowered by a solenoidal magnet fitting concentrically over the dilatometer bulb. Because of the closeness of fit of the stirrer to the dilatometer bulb wall, the dilatometer was slightly warmer than the thermostat. This heating effect was constant throughout any one run and could be evaluated by observing the meniscus rise associated with the stirring. In no case was the effective temperature of the dilatometer more than 0·1° above that of the thermostat.

(c) *Procedure.*—In order to fill the dilatometer and bring the monomer and catalyst together at exactly the right temperature, the following procedure was adopted: (i) The monomer was distilled into a graduated tube, and from there a known volume was distilled into the bottom of the dilatometer; once in the dilatometer, the α-methylstyrene was frozen and kept at liquid-air temperature until the start of the run. (ii) If water was to be added, this was distilled into the dilatometer next (see stannic chloride, below). (iii) The amount of ethyl chloride required to fill the dilatometer to a suitable level at the temperature of the experiment was then added: this was measured as vapour in a calibrated volume at known temperature and pressure. For dry runs or runs containing known quantities of added water, a sample of the ethyl chloride from the storage trap was condensed and evaporated several times from magnesium perchlorate at −78°. (iv) The stannic chloride catalyst was distilled into the dilatometer on top of the frozen ethyl chloride. The stannic chloride and the added water were measured by their respective pressures in a known volume. A glass Bourdon gauge was used as manometer. For experiments at very low catalyst concentrations (less than 4×10^{-1}M) the catalyst was premixed with ethyl chloride vapour in the ratio of 1 : 5 before measurement. (v) Whilst the monomer was kept frozen at the bottom of the dilatometer, the catalyst was mixed with approximately half the solvent by melting the ethyl chloride in the top part of the dilatometer. In this way it was possible to prevent the catalyst from concentrating in the capillary when the dilatometer was immersed into the thermostat.

The dilatometer was sealed *in vacuo* and kept in liquid air until required.

At the start of a run the dilatometer was completely immersed in a thermostat. No reaction could take place while temperature equilibrium was being reached since a thick layer of solvent separated the monomer from the catalyst. The initial reading of the miniscus was then taken, and the reaction started by setting the magnetic stirrer in motion. There was a slight volume change when the components were mixed which caused an error in the initial reading so obtained. In view of this, and in order to hasten the attainment of thermal equilibrium, the stirrer was started before thermal equilibrium was reached. This also reduced the possibility of any adventitious mixing of the monomer and catalyst. This method being used, the initial reading could be obtained with the aid of a slight extrapolation.

(d) *Polymer.*—In the majority of runs the reaction was carried to completion. The pure polymer from a given run was obtained by cutting off the top of the dilatometer, inverting it, and gently warming the dilatometer bulb. The boiling of the ethyl chloride then forced the contents of the dilatometer into a receiver. The solvent was removed from the polymer by evaporation at room temperature, followed by pumping to remove the final traces.

The polymers of low molecular weight were quantitatively separated as follows: About 0·3 g. of polymer was placed at the closed end of a horizontal Pyrex tube about 150 cm. long, made from 14-mm. bore tubing and containing constrictions every 3—4 cm. in order to prevent liquid flow along its length. This tube was then connected to the high-vacuum system in a horizontal position by means of a standard taper joint and evacuated. Around the glass tube was placed a heavy-walled copper tube, which was heated electrically to approximately 160° at the end containing the polymer and water-cooled at the opposite end. After several hours distinct bands of dimer, trimer, and tetramer were obtained along the length of the glass tube. The fractions were estimated by cutting the glass tube and weighing the sections. There were no signs of depolymerisation of the polymer when heated under these conditions.

(e) *Initial Rate of Shrinkage.*—For most of the experimental results the difference (x) between the dilatometric reading at any instant and the reading when the reaction had pro-

ceeded to completion decreased exponentially with time (t) according to the relation $x = x_0 e^{-kt}$, where x_0 is the total movement of the meniscus during the reaction. The dilatometric readings over the first 2 minutes, during which thermal equilibrium was disturbed by the stirring and then re-established, were sometimes in error, and in these cases the initial shrinkage rate was taken to be kx_0, since both k and x_0 could be accurately determined, from the dilatometer reading taken before stirring was begun and those taken subsequently.

(f) *Initial Rate of Reaction.*—If the polymer being formed throughout a given reaction has a constant density (due to constant composition or other cause) the shrinkage factor, defined as the concentration of monomer polymerised per unit length of meniscus movement, is equal to $[m_1]_0/x_0$, where $[m_1]_0$ is the initial value of the monomer concentration. It was not expected that this condition would be satisfied, since the di-, tri-, tetra-, and penta-mers differ considerably in density and are formed at different rates which vary as the reaction proceeds. However, estimates of the initial shrinkage factor based on comparison of the extent of meniscus fall for low known percentage conversions differed only slightly from $[m_1]_0/x_0$, *e.g.*, by 2%. Since errors of this magnitude are within the experimental error, it was considered reasonable to take $[m_1]_0/x_0$ as representing the true shrinkage factor.

(g) *Molecular Weights.*—The number-average molecular weights were determined cryoscopically in benzene or by calculation from the weight percentages of the various polymers when these components had been separated by the method described in section (d). The two methods gave comparable results. In some cases it was possible to analyse the polymer formed at several stages during a run and hence to extrapolate backwards to obtain an approximate value of the average molecular weight of the polymer forming at the start of the reaction.

(h) *Infra-red Spectra.*—Measurements were made with a Perkin–Elmer single-beam instrument by Dr. N. Sheppard, using methods appropriate to polymers of low molecular weight which are either liquid at room temperature or melt just above room temperature.

Results.—(a) *Properties of the polymers.* In general the properties of the various isolated polymers were as described by Staudinger and Breusch (*Ber.*, 1929, **62**, 442) except that the values of the refractive indices obtained by us were all about 0·002 unit higher than theirs. The dimer was a white crystalline solid, m. p. 52·0°, the melt of which supercooled to a much less dense liquid of n_D^{20} 1·5652 which was extremely reluctant to crystallise without seeding. The trimer was a clear amorphous solid, n_D^{20} 1·5875, which formed a viscous liquid at 25°. All the higher polymers were amorphous solids at room temperature.

The cryoscopically determined molecular weights of the various isolated polymers were exact multiples of the molecular weight of the monomer and therefore could not have contained adsorbed catalyst or chemically combined fragments of catalyst. No signs of unsaturation were detected in the polymer. Thus it did not enter into addition reactions, and the infra-red absorption spectrum showed no absorption in the regions characteristic of olefinic double bonds. The polymer was quite stable in the presence of the catalyst, neither undergoing further polymerisation, nor, if heated, depolymerising. This stability was not due to inactivation of the catalyst, which displayed its normal power of polymerising added monomer. Quite

TABLE 1. *Effect of water on rate of polymerisation of α-methylstyrene at 55°.*

(α-Methylstyrene, 0·56M; $SnCl_4$, 8·1 × 10⁻⁴M; shrinkage factor, 0·0910.)

Expt.	Methods of drying: * EtCl	Monomer	H_2O added, 10^{-4} mole $l.^{-1}$	Initial rate, 10^{-3} mole $l.^{-1}$ $l.^{-1}$ $min.^{-1}$	Expt.	Methods of drying: * EtCl	Monomer	H_2O added, 10^{-4} mole $l.^{-1}$	Initial rate, 10^{-3} mole $l.^{-1}$ $l.^{-1}$ $min.^{-1}$
32	A	—	—	7·50	49	C	—	—	2·50
33	A	—	—	7·68	47	C	—	4·1	11·3
36	A	—	16·0	7·68	44	C	—	8·1	9·2
37	A; also B	S	—	3·42	45	C	—	8·1	9·0
41	C	S	—	2·84	52	C	—	16·0	11·5
42	C	—	—	3·58	43	C	—	24·5	7·30
46	C	—	—	4·60	51	C	—	39·7	7·45
48	C	—	—	2·00	53	C	—	78·5	8·40

* (A) Distilled from solid CO_2 to liquid air. (B) Condensed and evaporated from P_2O_5 several times. (C) As for Expt. 37 except that $Mg(ClO_4)_2$ was used instead of P_2O_5. (S) Silica gel.

apart from the theoretical significance of these results (see p. 159), the saturated character of the polymer indicates that bromination is likely to be a highly unsuitable method for determining polymer molecular weights. Pepper, who used somewhat similar experimental conditions, obtained very erratic results by the bromination method, and we therefore think that his

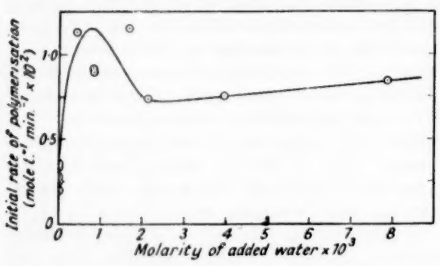
conclusions, based on this method, as to the dependence of the molecular weight of the polymer on the dielectric constant should be accepted with reserve.

(b) *Effect of water on the rate of polymerisation.* A series of experiments was carried out at 55° to determine the effect of added water on the rate of polymerisation. The experimental results are given in Table 1 and shown graphically in Fig. 1. Although the exact concentration of water in Expts. **32**, **33**, and **36** is not known, it seems reasonable to assume that it exceeded 5×10^{-3}M in view of the relatively ineffective method of drying the ethyl chloride.

The results show that water is probably a co-catalyst, and that as the drying is intensified the results become less reproducible. The latter feature is, no doubt, due to traces of remaining water, and it appears possible that no reaction would occur at all in a completely anhydrous system, as in the case of *iso*butene (Evans and Meadows, *Trans. Faraday Soc.*, **1950**, **46**, 327). When the ratio of added water to catalyst concentration is greater than about **3 : 1** the initial rate of polymerisation becomes independent of the amount of water present.

(c) *Effect of added deuterium oxide.* Further information concerning the mechanism of the co-catalytic action of water was obtained from experiments in which D_2O was used in place

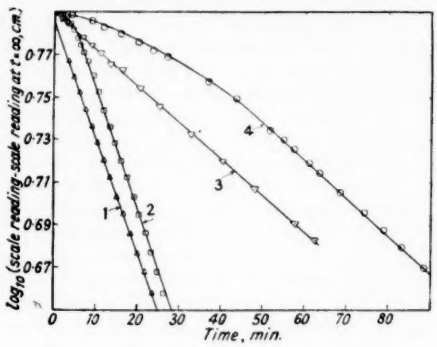
FIG. 1. *The effect of added water on the rate.*



$[m_1]_0 = 0{\cdot}56$M, $[SnCl_4]_0 = 0{\cdot}81 \times 10^{-3}$M, $T = 55°$ C.

Note that three other experiments, corresponding to an estimated water content greater than 5×10^{-3}M but which was not known with precision, gave rates of 0·752, 0·768, and $0{\cdot}768 \times 10^{-3}$ mole l.$^{-1}$.

FIG. 2. *The effect of added deuterium oxide on the rate.*



$[m_1]_0 = 0{\cdot}56$M, $T = 55°$C.

Curve 1: $[SnCl_4]_0 = 0{\cdot}81 \times 10^{-3}$M; $[H_2O]_0 = 1{\cdot}9 \times 10^{-3}$M.
„ 2: $[SnCl_4]_0 = 0{\cdot}81 \times 10^{-3}$M; $[D_2O]_0 = 3{\cdot}95 \times 10^{-3}$M.
„ 3: $[SnCl_4]_0 = 0{\cdot}40 \times 10^{-3}$M; $[H_2O]_0 = 3{\cdot}90 \times 10^{-3}$M.
„ 4: $[SnCl_4]_0 = 0{\cdot}40 \times 10^{-3}$M; $[D_2O]_0 = 3{\cdot}95 \times 10^{-3}$M.

of H_2O. The infra-red absorption spectra of the pure trimers obtained in the presence of the two waters were compared. The two types of spectra were identical except for an absorption band at 2180 cm.$^{-1}$ in the case of polymers formed in the presence of the D_2O. Since this is the frequency associated with the carbon–deuterium bond, it is assumed that some of the deuterium from the D_2O was incorporated into the polymer. This indicates that the initiating stage of the polymerisation is the donation of a proton (or deuteron) to the double bond of the monomer (cf. Dainton and Sutherland, *J. Polymer Sci.*, **1949**, **4**, 37).

The use of D_2O in place of H_2O as a co-catalyst modified the shrinkage rate in the first stages of the reaction, as illustrated by some typical curves in Fig. 2. The initial shrinkage rate is evidently less when D_2O is used than when H_2O is used, but the reaction accelerates and ultimately attains the rate characteristic of H_2O as a co-catalyst. It was at first considered possible that the cause of the acceleration was the destruction of some retarder in the D_2O. This explanation was rendered less likely by the fact that a fresh sample of 99·75% D_2O, which had previously been unopened and came from a different source, produced the same effect. It is hoped to study this phenomenon in greater detail later. For the present we tentatively regard it as a genuine isotopic effect, since, if it is true that the $SnCl_4$–D_2O complex initiates the polymerisation more slowly than the $SnCl_4$–H_2O complex, the acceleration can be accounted for. Any reaction mechanism which satisfies the minimum requirements of proton initiation and catalyst regeneration leads to the conclusion that the D_2O must be converted into H_2O,

and therefore that the reaction with D_2O as co-catalyst must continue to accelerate until all the D_2O has been so converted whereupon the rate characteristic of H_2O as co-catalyst will be reached but not exceeded. A corollary to this conclusion is that the number of molecules of polymer formed by the time the rate characteristic of H_2O as co-catalyst has been reached must exceed the number of D_2O molecules which was originally present in the catalyst–co-catalyst complex. This was always true. For example, in the experiment corresponding to curve 4 of Fig. 2, $3{\cdot}95 \times 10^{-5}$ mole of D_2O was originally present, and by the time the normal rate had been reached $\sim 7 \times 10^{-5}$ mole of polymer had been formed.

There is a little evidence that this effect of D_2O in reducing the rate in the early stages of the reaction reaches a maximum as more D_2O is added. Such a result would not be inconsistent with the saturation effect (Fig. 1) of H_2O on the rate. Both these phenomena can be accounted for if it is assumed that only a certain ratio of co-catalyst to catalyst is necessary for the reaction to attain its maximum rate, and that any additional water in excess of this ratio is not only redundant but for some unknown reason, which might be physical inhomogeneity, is unable to exchange protons with the water chemically bound to the catalyst.

(d) *Effect of catalyst–co-catalyst concentration.* It was soon evident that an increase of catalyst concentration caused a more than proportionate increase in the reaction rate, and experiments were therefore designed to determine the order with respect to catalyst concentration at several temperatures and as far as possible with sufficient co-catalyst present to ensure that slight variations of catalyst–co-catalyst ratio did not affect the rate, *i.e.*, in the level portion of Fig. 1. The results are summarised in Fig. 3, from which it is seen that at 0° the order is 1·54, at 25° it is 1·42, and at 55° 1·60. Whereas some of the points on curves 2 and 3 of Fig. 3 correspond to unknown water concentrations, the water content for all the experiments corresponding to points on Curve 1 was precisely known. We therefore conclude that at 0° and 0·56M-monomer, the order is 1·5 with respect to catalyst, and that this order probably prevails at other temperatures and monomer concentrations.

The effect of catalyst and co-catalyst concentration on the molecular weight of the polymer produced was investigated at 55°, a concentration of monomer of 0·56M being used. The results are given in Table 2, from which it may be seen that, although the initial rate varied by a factor of 7, the molecular weight was constant, corresponding to a degree of polymerisation of 2·5. This series of experiments, together with the molecular-weight data of other experiments not specifically designed to test this point, establish that for a given monomer concentration and temperature the degree of polymerisation is independent of the catalyst–co-catalyst concentration.

TABLE 2. *The effect of catalyst and co-catalyst concentration on the degree of polymerisation.* (*Monomer concentration* = 0·56M; *temp.* 55°.)

Catalyst concn., 10^{-4} mole $l.^{-1}$	Added H_2O, mole $l.^{-1}$	Initial rate, 10^{-3} mole $l.^{-1}$ $min.^{-1}$	Mol. wt. of polymer	Catalyst concn., 10^{-4} mole $l.^{-1}$	Added H_2O, mole $l.^{-1}$	Initial rate, 10^{-3} mole $l.^{-1}$ $min.^{-1}$	Mol. wt. of polymer
4·05	$3{\cdot}9 \times 10^{-3}$	2·36	298	8·10	$8{\cdot}1 \times 10^{-4}$	9·0	289 *
8·10	Normal drying	7·68	293	8·10	$4{\cdot}0 \times 10^{-4}$	11·3	298 *
8·10	Rigorous ,,	3·42	295	13·10	Normal drying	16·1	292
8·10	,, ,,	2·84	293				

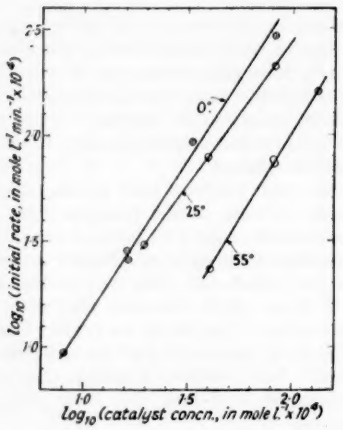
* Determined cryoscopically, the remainder by polymer analysis (see p. 152).

In all those experiments for which the number-average molecular weight of the polymer was measured, the ratio of the number of polymer molecules formed to the number of catalyst or co-catalyst molecules originally present greatly exceeded unity and in some cases was greater than 10^3.

(e) *Effect of monomer concentration.* A change of the monomer concentration affects both the molecular weight of the polymer and the rate of reaction. Since the degree of polymerisation is low and the relative shrinkage factors corresponding to formation of dimer, trimer, tetramer, and pentamer calculated from Staudinger's density data are in the ratio 1·00 : 1·35 : 1·44 : 1·45, the analysis of shrinkage–time curves at different monomer concentrations required a knowledge of the polymer composition–time curves. It was for this purpose that the polymer analysis procedure described in section (g) (p. 153) was devised. Although this procedure was accurate, it was too time-consuming to allow of obtaining a molecular weight distribution curve for successive stages of reaction for a series of experiments covering the whole range of conditions. Two expedients were therefore decided upon : (*a*) to analyse the polymer formed at low and at

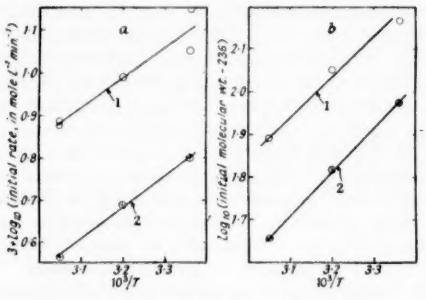
complete conversion in order to discover to what extent the number-average molecular weight changed throughout reaction, and (*b*) to investigate the reaction at lower temperatures under conditions where the higher molecular weights of the polymers formed would ensure a constant shrinkage factor during reaction. Experiments of the latter type will be reported in a later

FIG. 3. *The effect of catalyst concentration on the rate at different temperatures.*



$[m_1]_0 = 0{\cdot}56$M; $[H_2O]_0/[SnCl_4]_0 \geqslant 3$.

FIG. 4. *The effect of temperature on* (a) *initial rate and* (b) *the molecular weight of the polymer formed in the initial stages of reaction.*



Curves 1, $[m_1]_0 = 0{\cdot}56$M.
Curves 2, $[m_1]_0 = 0{\cdot}32$M.

publication. Table 3 illustrates the type of result obtained by experiments of the first type, and it will be seen that the molecular weight increases with monomer concentration. A feature of the graphs of initial molecular weight against monomer concentration is that if straight lines are drawn through the points the molecular weight at zero monomer concentration is always that of the dimer, irrespective of the temperature.

TABLE 3. *Effect of monomer concentration and temperature on the composition and molecular weight of polymer.*

Catalyst concn., $8{\cdot}1 \times 10^{-4}$M.

Temp.	Monomer concn., mole l.$^{-1}$	Polymer analysis, mol. % of: * (2)	(3)	(4)	(5)	(*x*)	*M* at 100% reaction	Approx. initial *M*
0°	0·56	—	—	—	—	—	415 †	—
25	0·32	29·0	62·0	9·0	—	—	330	330
25	0·56	18·0	71·0	10·0	1·0	—	347	384
25	0·56	15·0	72·0	12·0	1·0	—	356 ‡	—
25	0·80	15·0	65·0	9·0	9·0	2·0	374	453
40	0·32	46·0	51·0	3·0	—	—	303	303
40	0·56	30·5	68·5	1·0	—	—	323	350
55	0·32	62·5	37·5	—	—	—	281	281
55	0·56	51·5	48·5	—	—	—	293	313
55	0·56	50·5	49·5	—	—	—	295	315
55	0·56	—	—	—	—	—	289 †	—
55	0·56	—	—	—	—	—	298 †	—
100	0·56	88·0	12·0	—	—	—	251	—

* (2) = Dimer, (3) = trimer, (4) = tetramer, (5) = pentamer, (*x*) = high polymer.
† Determined cryoscopically. ‡ Analysis for 75% reaction.

The effect of monomer concentration on the initial rate, expressed as moles of monomer consumed per l. per min., is given in Table 4, due allowance having been made for the different shrinkage factors appropriate to the initial phases of each reaction. The values at 0° indicate an order with respect to monomer of unity at low concentrations which increases at higher concentrations and finally above 0·8M-concentration decreases again. This variation is outside the limits of experimental error. Although the same concentration range has not been covered, the data at other temperatures are more consistent with an order of unity at low concentrations,

rising above this value as the monomer concentration is increased, the average value of the order over the range studied being 1·4.

(f) *Effect of temperature.* From data already presented it can be seen that both the rate of reaction and the molecular weight of the polymer decrease with increasing temperature. In

TABLE 4. *Effect of monomer concentration on initial rate of reaction at various temperatures.*

Temp.	Monomer concn., mole l.$^{-1}$	Catalyst concn., 10^{-4} mole l.$^{-1}$	Initial rate, 10^{-3} mole l.$^{-1}$ min.$^{-1}$	Temp.	Monomer concn., mole l.$^{-1}$	Catalyst concn., 10^{-4} mole l.$^{-1}$	Initial rate, 10^{-3} mole l.$^{-1}$ min.$^{-1}$
0°	0·32	1·62 *	1·73	25°	0·56	8·1	11·2
0	0·40	1·62 *	2·20	25	0·56	8·1	14·1
0	0·56	1·62 *	2·84	25	0·80	8·1	21·2
0	0·56	1·62 *	2·56	40	0·32	8·1	4·9
0	0·68	1·62 *	6·71	40	0·56	8·1	9·69
0	0·80	1·62 *	10·6	55	0·32	8·1	3·67
0	1·20	1·62 *	18·3	55	0·56	8·1	7·50
0	1·92	1·62 *	19·4	55	0·56	8·1	7·68
25	0·32	8·1	6·25	55	0·56	8·1 †	7·30
25	0·40	8·1	7·03				

* Added water, $1·62 \times 10^{-3}$M. † Added water, $2·1 \times 10^{-3}$M.

Fig. 4 log (initial rate) and log (amount by which molecular weight of the polymer formed initially exceeds that of the dimer) for two different concentrations of monomer (0·32 and 0·56M) have been plotted against the reciprocal of the absolute temperature. The straight lines correspond to apparent Arrhenius energies of $E \sim -3·5$ kcal. for the rates and $E_M \sim -4·5$ kcal. for the molecular weights. The vertical displacements of the lines correspond to an order with respect to monomer of 4/3 and a direct proportionality between molecular weight and monomer concentration at any given temperature.

Other interesting features of the effect of temperature, clearly seen in Table 3, are that: (i) high polymers (*i.e.*, larger than the pentamer) are not formed at all at initial monomer concentrations below about 0·7M and temperatures greater than 25°, (ii) pentamers are not formed at 40° and higher temperatures for $[m_1]_0 < 0·56$M; (iii) at 55° tetramers cease to be formed, whereas (iv) trimers and dimers are formed up to at least 100°.

DISCUSSION

The kinetics of this reaction may be summarised by the equations:

$$-\mathrm{d}[m_1]/\mathrm{d}t = k_1[\mathrm{SnCl_4}]^{3/2}[m_1]^y \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and

$$\overline{\mathrm{DP}}_0 = 2 + k_2[m_1]_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where $[m_1]$ denotes monomer concentration; y increases from unity at low concentrations to higher values at higher concentrations; $k_1 = k_1^\circ \exp(3·5 \text{ kcal.}/\boldsymbol{RT})$; $k_2 = k_2^\circ \exp(4·5 \text{ kcal.}/\boldsymbol{RT})$ and is independent of $[\mathrm{SnCl_4}]$ under the conditions used, and $\overline{\mathrm{DP}}_0$ is the number-average degree of polymerisation corresponding to $[m_1]_0$. Water is an essential co-catalyst, and k_1 is therefore a function of $[\mathrm{H_2O}]$. However, provided the concentration of water is greater than roughly 3 times the catalyst concentration, which is the state of affairs when the usual methods of drying are employed, k_1 and the reaction rate are independent of $[\mathrm{H_2O}]$. The role of the co-catalyst is revealed by using $\mathrm{D_2O}$ as the catalyst, when C–D bonds are detected in the resultant polymer. It is concluded that the co-catalyst combines with the $\mathrm{SnCl_4}$ to form a compound of unspecified formula which initiates polymerisation by donating a proton to a monomer molecule, thereby converting the latter into a carbonium ion of probable formula $(\mathrm{CH_3})_2\overset{+}{\mathrm{C}}\cdot\mathrm{C_6H_5}$. The fact that the number of polymer molecules formed in a reaction greatly exceeds the number of co-catalyst molecules initially present implies that the latter are regenerated, and that the termination reaction is one of proton expulsion, the proton being ultimately returned to an anionic fragment of the catalyst–co-catalyst compound. The lag phase observed when $\mathrm{D_2O}$ is used as a co-catalyst is in harmony with this mechanism. Two conclusions may be drawn

from the results expressed in equation (2): (*a*) that chain transfer to monomer does not occur, and (*b*) that the rate of the proton-repulsion process involved in chain termination is independent of both the catalyst and monomer concentrations. We may therefore write the reaction mechanism in the form

$$\text{Initiation}: \quad A + m_1 \longrightarrow A^- + m_1^+ \ (k_i) \qquad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$\text{Propagation}: \quad m_1^+ m_j^+ \longrightarrow m^+_{j+1} \ (k_{p,j}) \qquad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$\text{Termination}: \quad m_j^+ \longrightarrow H^+ + P_j \ (k_{t,j}) \qquad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where m_1 denotes monomer, A the catalyst–co-catalyst complex providing the protons, m_j^+ the growing polymer carbonium ion containing j monomeric segments, and P_j the dead polymer containing j monomeric units. The most obvious objection to this simple scheme is that it predicts that the reaction rate will be proportional to [A], and it is natural to assume that [A] is in turn proportional to an integral power of the catalyst concentration. However, the observed exponent of the catalyst concentration in the expression for the rate is 1·5. This exponent is the most unusual feature of the reaction, since in most ionic polymerisations the exponent is unity. In one case where it exceeds unity, namely, the iodine-catalysed polymerisation of octyl vinyl ether (Eley and Richards, *Trans. Faraday Soc.*, 1949, **45**, 425), the observed exponent of 2 was readily accounted for by assuming the chain initiator to be the I^+ ion in equilibrium with iodine molecules according to $2I_2 \rightleftharpoons I^+ + I_3^-$. In the present case the corresponding equilibrium might be

$$3SnCl_4 + 2H_2O \rightleftharpoons 2H^+ + Sn_3Cl_{12}(OH)_2 \qquad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

and a plausible structure for the anion is readily formulated. However, no special significance can be attached to equation (6), and for the present we merely write $[A] = K[SnCl_4]^{2/3}$, in order to satisfy equation (1). The expression for the reaction rate deduced from the mechanism is

$$-\frac{d[m_1]}{dt} = k_i[m_1][A]\frac{k_{p_1}[m_1]}{k_{p_1}[m_1] + k_{t_1}}\left\{2 + \sum_{j=1}^{j=\infty} \pi\left(\frac{k_{p,j}[m_1]}{k_{p,j+1}[m_1] + k_{t,j+1}}\right)\right\} \quad . \quad (7)$$

and if we assume that the velocity constants k_p and k_t are independent of j, this becomes by summation of the convergent series

$$-\frac{d[m_1]}{dt} = k_i[m_1][A]\frac{k_p[m_1]}{k_p[m_1] + k_t}\left\{1 + \frac{1}{1 - \dfrac{k_p[m_1]}{k_p[m_1] + k_t}}\right\}$$

$$= k_i[m_1][A]\frac{k_p[m_1]}{k_p[m_1] + k_t}\left\{2 + \frac{k_p[m_1]}{k_t}\right\} \quad . \quad (8)$$

When high polymers are formed $k_p[m_1] \gg k_t$, and equation (8) reduces to the familiar form

$$-d[m_1]/dt = (k_i k_p/k_t)[A][m_1]^2$$

However, the reaction is of less than second order with respect to monomer, and this is due to the fact that only polymers of low molecular weight are formed so that $k_p[m_1]$ is of the same order of magnitude as k_t. On closer examination equation (8) is seen not to express the observed variation of the rate with change of monomer concentration. Much closer accord with experiment may be achieved by omitting k_t from the term outside the bracket. It will be recalled that this k_t is really k_{t_1} [of equation (7)], and putting it equal to zero is equivalent to stating that the monomeric ion m_1^+ does not spontaneously expel a proton and that either (*a*) all monomeric ions formed in the initiation reaction react to form a dimer, or (*b*) a large proportion revert to $A + m_1$. The two cases (*a*) and (*b*) correspond to values of $[m_1^+]$ of $k_i[A]/k_{p_1}$ and $(K[A][m_1])^{\frac{1}{2}}$, respectively, where K is the equilibrium constant of the ionisation reaction (3). The present data do not permit a decision between these two possibilities, although the data at 0° suggest that the order with respect to

monomer may exceed 1·5. Writing $V_{init.}$ for reaction (3), thereby deliberately leaving open the question of the initiation mechanism, we find for the rate equation

$$-\mathrm{d}(m_1)/\mathrm{d}t = V_{init.}\{2 + k_p(m_1)/k_t\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

from which we deduce

$$\overline{\mathrm{DP}}_0 = [2 + k_p(m_1)]/k_t \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

The rather meagre data available are in accord with equation (11) and may be used to show that $E_t - E_p = 4{\cdot}5$ kcal. and $k_p/k_t = 1{\cdot}2 \times 10^{-3} \cdot \exp(4{\cdot}5/RT)$ l. mole^{-1}. The apparent overall activation energy E_R should, according to equation (10), decrease from a value $= E_i + \frac{1}{2}\Delta H_6$ at low monomer concentrations to a limiting value of $E_i + \frac{1}{2}\Delta H_6 + (E_p - E_t)$ at higher monomer concentrations. The observed value of E_R is $-3{\cdot}5$ kcal., and therefore the maximum value of $E_i + \frac{1}{2}\Delta H_6$ is 1 kcal., which, although small, is not inconsistent with the findings in other ionic polymerisations; *e.g.*, Plesch (*Sci. Proc. Roy. Dublin Soc.*, 1950, **25**, 154) has found that the highest possible value of E_i in the $TiCl_4$–H_2O-catalysed polymerisation of *iso*butene is 4 kcal., and the probable value is much smaller.

In the foregoing paragraphs no reference has been made to the saturated structure of the polymer formed. When Tiffeneau (*Ann. Chim. Phys.*, 1907, **10**, 158) first prepared the saturated dimer of α-methylstyrene, he concluded that it was 1 : 3-dimethyl-1 : 3-diphenyl*cyclo*butane. Staudinger and Breusch concurred in this view and also concluded that the higher polymers which they isolated were large alicyclic compounds. More recently, Bergmann, Taubadel, and Weiss (*Ber.*, 1931, **64**, 1493) re-examined the saturated dimer and concluded that it is in fact 1 : 1 : 3-trimethyl-3-phenylindane, suggesting that formation of the saturated dimer proceeded *via* the unsaturated dimer, 1 : 3 : 3-trimethyl-1 : 3-diphenylpropene [4-methyl-2 : 4-diphenylpent-2-ene].

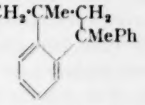
There is also little doubt that under suitable conditions unsaturated polymers of α-methylstyrene can be prepared by using, *e.g.*, phosphoric acid, floridin (Klages, *Ber.*, 1902, **35**, 2639; Lebedev and Filonenko, *Ber.*, 1925, **58**, *B*, 163), or even stannic chloride as catalyst. These facts can be reconciled by regarding the normal fast termination reaction as proton expulsion from the β-carbon atom to form the unsaturated polymer (I) which is capable of rearrangement to form a saturated polymer (II) containing a 1 : 3-dimethyl-3-phenylindanyl end group :

$$\mathrm{CMe_2Ph{\cdot}[CH_2{\cdot}CMePh]_{\mathit{j}-1}{\cdot}CH{:}CMePh + H^+} \quad \text{(I)}$$

$$\downarrow$$

$$\mathrm{CMe_2Ph{\cdot}[CH_2{\cdot}CMePh]_{\mathit{j}}{}^+} \quad \text{(III)}$$

$$\mathrm{CMe_2Ph{\cdot}[CH_2{\cdot}CMePh]_{\mathit{j}-2}{\cdot}CH_2{\cdot}CMe{\cdot}CH_2}$$



(II)

It would be expected that this rearrangement would be catalysed by the catalyst–co-catalyst complex [possibly proceeding *via* the carbonium ion (III)], and if the energy of activation is appreciable the proportion of unsaturated polymer formed would be larger the lower the temperature. Although no quantitative data exist for adequate testing of this prediction, it is in harmony with the qualitative data available.

The possibility that D_2O is a less effective co-catalyst than H_2O has been mentioned and, in view of the reaction mechanism proposed, the difference is probably due to the different rates of abstraction by the monomer of H^+ and D^+ from the catalyst–co-catalyst complex. Although isotopic influences of this kind have not hitherto been observed in ionic polymerisations, they have been recognised in acid–base catalysis (Bell, " Acid Base Catalysis," Oxford, 1949, pp. 143—152). It is hoped to investigate this aspect of the reaction in detail later.

The very steep decrease of both the rate and the molecular weight with increasing temperature, which is the feature of polymerisation reactions in which depropagation is occurring to an appreciable extent, has not been observed in this system. This was an unexpected result, since at the monomer concentrations (~1M) used, the ceiling temperature for high-polymer formation would have been expected to be about room temperature. However, Jessup's data show that $\Delta H°_{lc}$ for α-methylstyrene polymerisation increases

markedly with decreasing chain length of the polymer when this is less than 10. Accordingly, the ceiling temperatures for pentamer, trimer, and dimer (the principal products in these experiments) are likely to increase in the order given, and all to be above room temperature. Depropagation, *i.e.*, reversal of the reaction given in equation (4), will therefore be unimportant in these experiments for values of $j < 6$. The proton-expulsion reaction (5) is thus the most important factor determining the overall rate and degree of polymerisation.

The authors are indebted to the National Research Council of Canada for a post-doctoral fellowship awarded to R. H. T.; to Professor R. G. W. Norrish for the facilities of the Department of Physical Chemistry, Cambridge, where the experimental work was carried out, to the Distillers' Company Ltd. for the gift of a sample of α-methylstyrene, and to Dr. N. Sheppard for advice and measurement of infra-red spectra.

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32. *Synthetic Œstrogens. Part I. The Synthesis of* 2 : 3-*Di*-p-*hydroxyphenyl*-2 : 3-*dimethylbutane, an Isomer of Hexœstrol.*

By R. L. HUANG and FRANCIS MORSINGH.

The diphenol named in the title has been synthesised by three methods, all involving dimerisation of free radicals. It has low solubility in aqueous alkalis, exhibits the unusual property of evolving methyl iodide under the conditions of the Zeisel determination, and is only weakly œstrogenic.

THE " structural resemblance " theory of synthetic œstrogens (Dodds, Goldberg, Lawson, and Robinson, *Proc. Roy. Soc.*, 1939, *B*, **127**, 140), although probably an over-simplification, stimulated the present research. The diphenyl-ethane and -ethylene series contain several patent synthetic hormones of wide clinical application (stilbœstrol, hexœstrol, dienœstrol). Substances of the type *p*-HO·C_6H_4·CHR·CHR′·C_6H_4·OH-*p* so far investigated have all contained the –CHR·CHR′– group corresponding to the B–C ring junction of natural steroids. If, however, a third or a fourth alkyl group were introduced, to give the grouping $-CR^1R^2\cdot CR^3R^4-$ (R^4 = H or alkyl), the structure would bear less resemblance to œstradiol. 2 : 3-Di-*p*-hydroxyphenyl-2-methylpentane (I; R = Me) and 3 : 4-di-*p*-hydroxyphenyl-3-methylhexane (I; R = Et) have been prepared (Huang, Thesis, Oxford, 1947) and found to be highly potent (full response in rats at dosages of 1 and 0·5 γ respectively). We therefore prepared the tetra-methyl homologue 2 : 3-di-*p*-hydroxyphenyl-2 : 3-dimethylbutane (II), which is isomeric with hexœstrol.

(I) *p*-HO·C_6H_4·CRMe·CHEt·C_6H_4·OH-*p* *p*-HO·C_6H_4·CMe_2·CMe_2·C_6H_4·OH-*p* (II)

Normal methods are not suited for the preparation of fully substituted dibenzyls typified by (II). For instance, in an approach to a Wurtz reaction, attempts to obtain pure 3-chloro-3-*p*-methoxyphenylpentane gave only the olefin (Huang, unpublished work). However, Kharasch, McBay, and Urry (*J. Org. Chem.*, 1945, **10**, 401) prepared 2 : 3-dimethyl-2 : 3-diphenylbutane, the unhydroxylated analogue of (II), by dimerisation of the radical obtained from *iso*propylbenzene by acetyl peroxide. We have prepared (II) by three methods, each involving dimerisation of a free radical which, however, we prepared by means of the safer di-*tert.*-butyl peroxide (Farmer and Moore, *J.*, 1951, 131).

First, 2-*p*-methoxyphenylpropan-2-ol was dehydrated by heat in the presence of a small quantity of quinol, and the resulting olefin reduced with sodium in ethanol to *p-iso*propylanisole. (The olefin polymerised readily in the presence of proton donors, *e.g.*, halogen or sulphuric acids, or free-radical initiators, *e.g.*, iodine.) Dimerisation of *p-iso*propylanisole by heating it with di-*tert.*-butyl peroxide at 140° under reflux or in a Carius tube (Farmer

and Moore, *loc. cit.*) and demethylation with hydrobromic acid, gave the desired diphenol (II). This product, although apparently pure, gave a small but definite value for methoxyl in the Zeisel determination. However, demethylation by hydriodic acid or methylmagnesium iodide yielded the same product as obtained above. Accordingly, the methoxyl group was then removed at an earlier stage : *p-iso*propylanisole was demethylated to *p-iso*propylphenol, the benzoate of which on dimerisation and subsequent hydrolysis afforded the same diphenol (II). Finally, in a synthesis avoiding the methoxyl group altogether, 2 : 3-dimethyl-2 : 3-diphenylbutane (Farmer and Moore, *loc. cit.*) was successively nitrated, reduced, and subjected to a diazo-reaction, once more yielding (II).

It has further been established that a number of fully methylated dibenzyls analogous to (II) yield methyl iodide under the conditions of the Zeisel determination (Huang and Morsingh, *Analyt. Chem.*, **1952**, **24**, 1359).

The substance (II) is relatively insoluble in aqueous alkali. It is only weakly active as an œstrogen (10 mg. for full response in castrated rats).

Experimental

M. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford.

p-iso*Propylanisole*.—Crude 2-*p*-methoxyphenylpropan-2-ol (55 g.) (from *p*-methoxyphenylmagnesium bromide and acetone) was heated with quinol (0·1 g.) at 110°/vac. for 30 minutes. Water separated. Distillation afforded the olefin (40 g.), b. p. 86°/2 mm., n_D^{25} 1·5483. By this treatment the dimeric product reported by Behal and Tiffeneau (*Compt. rend.*, 1901, **132**, 561) was not encountered. The olefin (34 g.) was then reduced with sodium in ethanol in the usual manner, giving the required *p-iso*propylanisole (15 g.), b. p. 55—58°/2 mm., n_D^{23} 1·5032. Klages (*Ber.*, 1904, **37**, 3996) reports b. p. 95—96°/19 mm., n_D^{17} 1·5045.

2 : 3-*Di*-p-*methoxyphenyl*-2 : 3-*dimethylbutane*.—(*a*) *p-iso*Propylanisole (15 g.) and di-*tert*.-butyl peroxide (7·5 g.; Milas and Surgenor, *J. Amer. Chem. Soc.*, 1946, **68**, 205) were heated under reflux at 140—145° for 48 hours, under a slow stream of nitrogen. Distillation removed *tert*.-butanol, b. p. 44°/100 mm. (4 g.), and unchanged hydrocarbon, b. p. 55°/2 mm. (9·4 g.). The residue, a dark brown glass, freely soluble in benzene but sparingly soluble in light petroleum, was chromatographed in benzene, on alumina. Elution with benzene–light petroleum (1 : 4) gave 2 : 3-*di*-p-*methoxyphenyl*-2 : 3-*dimethylbutane* (3·0 g., crude) which recrystallised from benzene–ethanol in prisms, m. p. 183—185° (0·44 g.) (Found : C, 80·2; H, 8·7. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·8%).

(*b*) *p-iso*Propylanisole (4 g.) and di-*tert*.-butyl peroxide (2 g.) were heated under nitrogen in a sealed tube at 150—155° for 26 hours. After addition of a few drops of petroleum yellowish crystals were deposited during 24 hours. These on trituration with ethanol followed by three recrystallisations from benzene–ethanol afforded the butane derivative, m. p. 183—185° (0·40 g.).

2 : 3-*Di*-p-*hydroxyphenyl*-2 : 3-*dimethylbutane*.—The above product (87 mg.) was heated under reflux with hydrobromic acid (*d* 1·5; 1 ml.) and acetic acid (7 ml.) for 8 hours. The mixture was poured into water and extracted with ether. The ethereal solution was washed several times with sodium hydrogen carbonate solution, water, and finally 5% aqueous sodium hydroxide. After being washed with ether, the alkaline extract was acidified and the precipitated *diphenol* recovered in ether and crystallised from benzene as needles, m. p. 205—210° (50 mg.), raised to 210—212° by two recrystallisations from *cyclo*hexane (Found: C, 80·0; H, 8·2; OMe, 3·1. $C_{18}H_{22}O_2$ requires C, 80·0; H, 8·15; OMe, 0%). Approx. 0·1 g. dissolved in 100 ml. of 10% aqueous sodium hydroxide. The compound forms a *dibenzoate*, leaflets (from ethyl acetate–benzene), m. p. 251° (Found : C, 80·4; H, 6·4. $C_{32}H_{30}O_4$ requires C, 80·3; H, 6·3%).

Demethylation by hydriodic acid (*d* 1·7) and acetic acid (1 : 3) for 4 hours, or by methylmagnesium iodide at 180—190° for 1¼ hours, gave the same product, m. p. and mixed m. p. 210—212°. The latter product still gave an apparent methoxyl value (OMe, 3·8, 4·3%).

Dimerisation of p-iso*Propylphenyl Benzoate*.—*p-iso*Propylanisole (12·7 g.) was demethylated with hydrobromic–acetic acid, and the phenol converted into the benzoate which, recrystallised twice from ethanol, formed needles, m. p. 69—70° (6·0 g.). Behal and Tiffeneau (*Bull. Soc. chim.*, 1908, **3**, 318) report m. p. 70—71°. This (6·0 g.) was heated with di-*tert*.-butyl peroxide (3·2 g.) in a sealed tube as described above. The mixture on cooling deposited crystals which

were washed with ether (the dimer is sparingly soluble in contrast to the monomer). On recrystallisation from ethyl acetate, 2 : 3-di-*p*-benzoyloxyphenyl-2 : 3-dimethylbutane had m. p. 245—247° (2·3 g.), raised to m. p. 251° after further recrystallisation.

2 : 3-*Di*-p-*hydroxyphenyl*-2 : 3-*dimethylbutane*.—The above dibenzoate (1·14 g.) in warm benzene (20 ml.) was heated with 5% ethanolic sodium hydroxide (200 ml.) under reflux for 7 hours. The solvents were removed, leaving the solid sodium salt of the required diphenol. Water (70 ml.) was added, and the sparingly soluble sodium salt separated at the centrifuge. It was then acidified with hydrochloric acid and the liberated diphenol taken up in ether (80 ml.) and worked up in the usual way, yielding a pure product, m. p. 212° (0·41 g.).

2 : 3-*Dimethyl*-2 : 3-*di*-p-*nitrophenylbutane*.—2 : 3-Dimethyl-2 : 3-diphenylbutane (4·0 g.) was cautiously added to concentrated nitric acid (25 ml.; *d* 1·42), and the mixture heated with stirring at 70—80° for 7 hours, after which a yellowish-orange colour had developed. The cooled mixture was poured into ice-water, and the yellowish-orange solid which separated was washed with water by decantation, treated with a small quantity of hot ethanol, which removed most of the yellow colour, and repeatedly extracted with boiling chloroform. Thereby a chloroform-insoluble and a chloroform-soluble fraction were obtained. The former was 2 : 3-*dimethyl*-2 : 3-*di*-p-*nitrophenylbutane*, a yellowish powder (1·5 g.), m. p. 265° (decomp.) (Found : C, 65·5; H, 5·9; N, 8·45. $C_{18}H_{20}O_4N_2$ requires C, 65·8; H, 6·1; N, 8·5%). The combined chloroform filtrates were concentrated to approx. 15 ml. Thereupon another yellowish solid, m. p. 230° (0·6 g.), separated, probably the op′-*isomer* (Found : C, 65·6; H, 6·0; N, 8·2%). Both compounds are sparingly soluble in ethanol, acetone, light petroleum, and ethyl acetate.

2 : 3-*Di*-p-*aminophenyl*-2 : 3-*dimethylbutane*.—The *pp*′-dinitro-compound (1·5 g.) was heated under reflux with ethanol (160 ml.) and concentrated hydrochloric acid (4 ml.) while iron filings (4 × 1·5 g.) were introduced during 20 minutes, and vigorous refluxing was continued for 10 hours. The mixture was then made neutral with alcoholic sodium hydroxide (excess being avoided) and filtered hot. The residue was washed with boiling ethanol. The combined filtrates on concentration afforded 2 : 3-*di*-p-*aminophenyl*-2 : 3-*dimethylbutane* (1·2 g.) which was washed with water. After four recrystallisations from benzene (charcoal) it was obtained as prisms, m. p. 235—236° (Found : C, 80·4; H, 8·7; N, 10·4. $C_{18}H_{24}N_2$ requires C, 80·6; H, 8·95; N, 10·45%), insoluble in water, but soluble in dilute hydrochloric acid. The Schotten–Baumann technique gave a dibenzoate, m. p. >270°.

2 : 3-*Di*-p-*hydroxyphenyl*-2 : 3-*dimethylbutane*.—Burger and Mosettig's method (*J. Amer. Chem. Soc.*, 1937, **59**, 1304) for conversion of an amine into a phenol was unsuitable. DeMilt and Van Zandt's method (*ibid.*, 1936, **58**, 2044) was used : Sodium nitrite (1·5 g.) was added to dilute sulphuric acid (15 ml. of concentrated acid in 7·5 ml. of water) and the mixture heated with stirring on a steam-bath until a clear solution of nitrosylsulphuric acid was obtained. This was then cooled to 0° and stirred mechanically as the diamine (220 mg.) in pyridine (5 ml.) was added during an hour, after which stirring was continued for another hour at 0°. The solution was then diluted to 200 ml. by ice-water, and treated with urea (1 g.) in water (25 ml.). After a further hour's stirring at 0°, more water (200 ml.) was added and the mixture boiled until decomposition was complete. A yellowish-orange solution was obtained which when cooled was extracted with ether, and the diphenol isolated from the ethereal extract in the usual manner. Recrystallisation from benzene yielded the pure substance, m. p. and mixed m. p. 210° (62 mg.).

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33. *Hydrated Calcium Silicates. Part V.* The Water Content of Calcium Silicate Hydrate* (I).

By H. F. W. Taylor.

The water content of calcium silicate hydrate (I), (1—1·5CaO,SiO_2,xH_2O), has been investigated, principally by dehydration isobars and *X*-ray photographs of samples partly or fully dehydrated under various conditions. Laboratory preparations, made by four different methods, and natural riversideite, have been studied. Three distinct states of hydration exist, having $x = 2{\cdot}5$ approx., 1·0, and 0·5, and *c*- or inter-layer spacings of 14·0, 10·4, and 9·3 Å, respectively. The *a*- and *b*-axes are unaffected during dehydration to the monohydrate, but further dehydration causes them to shrink slightly, and it is probable that one molecule of water is essential to the structure of the layers. The expelled water can be replaced completely if the water content has not been reduced below 1·0, but there is a marked hysteresis effect, and the original *c*-spacing is not fully regained. The water : silica ratio *x*, after any given conditions of dehydration, is independent of the lime : silica ratio of the sample. This seems to rule out the theory that the variable lime content is due to adsorption of calcium hydroxide. The products formed on complete dehydration have been investigated; at 800°, β-wollastonite is formed. A high degree of order is maintained throughout the dehydration process, and a structural resemblance must exist between calcium silicate hydrate (I) and β-wollastonite.

In Part I (*J.*, 1950, 3682), the preparation at room temperature of calcium silicate hydrate (I) was described, and it was shown to have a variable composition, approximating to 1·0—1·5CaO, SiO_2,xH_2O, and a layer structure showing certain similarities to those of the clay minerals. The present paper deals with the water content *x* of this substance, including the dependence of this quantity on the lime : silica ratio, and on the conditions of temperature and humidity, and with its relation to the spacing between the layers within the crystal.

Previous Investigations.—A few investigations of a limited character are on record. For samples of lime : silica ratio 1 : 1, the water content, after the substance had been brought into equilibrium with an atmosphere of ordinary temperature and humidity ($p_{H_2O} \simeq 10$ mm. of Hg), is in the region of 2—2·5 (Le Chatelier, *Ann. Mines*, 1887, **11**, 345; Bessey, "Symposium on the Chemistry of Cements," Stockholm, 1938, p. 178; Hedin, "Chemical Processes in the Hardening of Portland Cement," Stockholm, 1945; Brocard, *Ann. Inst. Tech. Batiment*, 1948, No. 1, 1). This is reduced to approximately 1·0 by drying over calcium oxide at room temperature (Keevil and Thorvaldson, *Canadian J. Res.*, 1936, **14**, *B*, 20; Bessey, *op. cit.*), by heating to 100—150° (Cirilli, *Ann. Chim. appl.*, 1938, **28**, 239; Forsen, "Symposium on the Chemistry of Cements," Stockholm, 1938, p. 298; Hedin, *loc. cit.*), or by extraction of loosely held water with liquid ammonia (Thilo, Funk, and Wichmann, *Abhand. Deut. Akad. Wiss. Berlin*, 1950, No. 4, 1). On the basis of such evidence, Roller and Ervin (*J. Amer. Chem. Soc.*, 1940, **62**, 461) and Thilo (*Angew. Chem.*, 1951, 201) considered the composition of calcium silicate hydrate (I) to be CaH_2SiO_4.

Somewhat contradictory results have been obtained for samples of higher lime : silica ratio. Lefol (*Compt. rend.*, 1935, **201**, 669) found the dehydration isotherm, for a sample of composition 1·2CaO,SiO_2,xH_2O, to be a smooth curve, in agreement with that obtained by Bessey (*op. cit.*) for one of composition CaO,SiO_2,xH_2O. On the other hand, Cirilli (*Ric. Sci.*, 1939, **10**, 459) and Hedin (*loc. cit.*) reported values of the water content, after given conditions of dehydration, which were markedly dependent upon the lime : silica ratio.

In none of the heating experiments mentioned above does any attempt appear to have been made to control the humidity of the atmosphere with which the substance was in contact. The results obtained from them are therefore of uncertain significance. No attempts to correlate variations in water content with *X*-ray spacings have been reported.

Considerable help was given in the present investigation by the recent observation

* Part IV, *J.*, 1952, 2535.

(Taylor, *Min. Mag.*, in the press) that natural riversideite is a close fibrous intergrowth of an apatite mineral, wilkeite, with calcium silicate hydrate (I). The latter, despite the presence of the wilkeite, is in a physical state more amenable to crystallographic investigation than in any of the laboratory preparations so far made. This enabled more detailed results to be obtained than would otherwise have been possible.

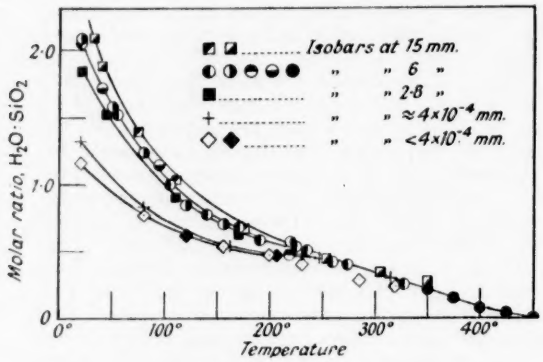
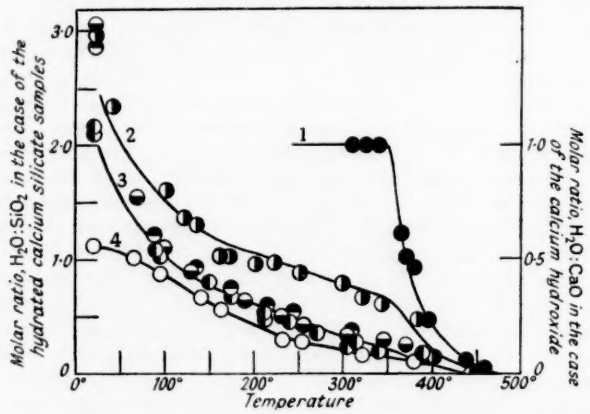


FIG. 1. *Dehydration isobars for calcium silicate hydrate* (I). *Effect of variation in the partial pressure of water vapour*: *Sample* (1), CaO : SiO_2 = 0·99.

Each type of point represents a separate experiment. Full curves are drawn through the points for each isobar separately up to *ca.* 230°; at higher temperatures, only a single curve, for pressure 6 mm., is drawn.

FIG. 2. *Dehydration isobars for several preparations of calcium silicate hydrate* (I), *and for calcium hydroxide. Partial pressure of water vapour* = 6 *mm.*



1. —●— *Calcium hydroxide.*
◑ *Sample* 7. CaO : SiO_2 = 1·95.
2. —— *Calculated for* 1 *mol. of calcium silicate hydrate* (I) +0·45 *mol. of calcium hydroxide.*
3. —— *Sample* 1. CaO : SiO_2 = 0·99.
◒ *Sample* 9. CaO : SiO_2 = 1·37.
◐ *Sample* 2. CaO : SiO_2 = 1·30.
◓ *Sample* 6. CaO : SiO_2 = 1·24.
4. —○— *Sample* 10. (*Hydrothermal preparation.*)

Results.—(1) *Dehydration isobars for a sample of composition* CaO,SiO_2,xH_2O : *effect of variation in pressure.* A series of isobars, obtained at different partial pressures of water vapour, is shown in Fig. 1. The sample was made at room temperature by reaction between calcium hydroxide solution and silica gel (Part I, *loc. cit.*). The results confirm earlier indications that about 1·0 mol. of water remains after heating to 100° under normal conditions of humidity, or after standing over powerful dehydrating agents at room temperature. They do not, however, give any indication of the existence of a definite hydrate of this composition. On the other hand, the isobars all show a point of inflection, in the neighbourhood of 220°, possibly indicating the existence of a hemihydrate.

(2) *Dehydration isobars for various samples of approximate composition* CaO,SiO_2,xH_2O. In order to test reproducibility, isobars at 6 mm. pressure of water vapour were obtained for five additional samples having lime : silica ratios near 1 : 1. Four of these gave results in close agreement with those already described; each of these had been prepared at room temperature, either by double decomposition of calcium nitrate and sodium silicate (nos. 3, 4, and 5) or by the action of water on Ca_3SiO_5 (no. 8). Reproducible results are thus obtainable for samples made at room temperature, irrespective of the method of preparation. The fifth sample (no. 10), prepared hydrothermally (Part II, *J.*, 1951, 2397), gave a curve (Fig. 2) which was not very different from the others at 100° and above, but showed a much lower water content at room temperature, the curve tending to a distinct limit at a water content of about 1 : 1. In this case, therefore, there is some indication that a monohydrate may exist.

(3) *Dehydration isobar for natural riversideite.* This is shown in Fig. 3. The isobar, obtained at 6 mm. pressure, shows distinct points of inflection at temperatures in the neighbourhood of 100° and 220°. Owing to the difficulties of obtaining a pure sample, or in making allowance for the impurities present (Taylor, *Min. Mag.*, *loc. cit.*), the values of the water content corresponding to these points of inflection are approximate. The water contents at 100° and 220° are 0·8 and 0·5, respectively. The first of these corresponds very roughly with the water content, below 100°, of the hydrothermal preparation already

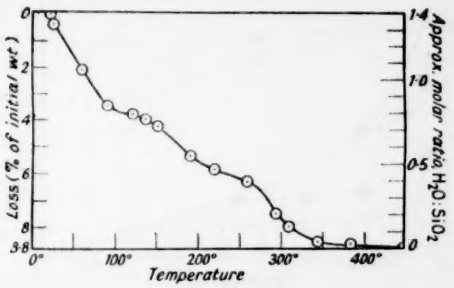


FIG. 3. *Dehydration isobar for natural riversideite. Partial pressure of water vapour = 6 mm.*

described, and the second corresponds with the point of inflection at 220° and 0·5 mol. shown in varying degrees by all the artificial samples.

(4) *Dehydration isobars for samples of calcium silicate hydrate* (I) *having varying molar ratios of lime to silica.* Fig. 2 includes data for three samples having lime : silica molar ratios (y) within the range 1·0 : 1 and 1·5 : 1. All had been prepared at room temperatures : one had been made by double decomposition, and had $y = 1·24$; a second was prepared from calcium hydroxide and silica gel, and had $y = 1·30$; the third was obtained from tricalcium silicate and had $y = 1·37$. The dehydration isobars of all three are in close agreement with those of the samples having $y = 1·0$. For samples prepared at room temperature, therefore, the water content x at any given temperature and pressure is independent, within the limits of error of the present experiments, both of the method of preparation and of the molar lime : silica ratio y.

(5) *Dehydration isobars for calcium hydroxide, and for a mixture of calcium hydroxide with calcium silicate hydrate* (I). Attempts to prepare samples of the hydrate (I) having lime : silica ratios in excess of 1·5 : 1 yield, at least at room temperature, mixtures of this substance with calcium hydroxide (Part I, *loc. cit.*). The dehydration isobar, at 6 mm. pressure, for one such sample is included in Fig. 2. The sample was prepared by double decomposition, and had an overall lime : silica molar ratio of 1·95 : 1. For the purpose of comparison, a dehydration isobar for calcium hydroxide was obtained at the same pressure (Fig. 2). It will be seen that almost all the water in this compound is lost within the range 350—450°. This is in close agreement with the results obtained by Krauss and Jörns at 7 mm. (*Zement*, 1931, **20**, 314, 341). Curve 2 in Fig. 2 was calculated by adding together at each temperature the observed water contents for 1·0 mol. of calcium silicate hydrate (I), of composition $1·5CaO,SiO_2,xH_2O$, and 0·45 mol. of calcium hydroxide. The close agree-

ment with the experimental points for the sample of lime : silica ratio 1·95 : 1 shows that the lime in excess of 1·5 mol. in the latter is present in the form of hydroxide.

(6) *Rehydration of calcium silicate hydrate* (I) *on cooling from various temperatures.* Fig. 4 shows the results of attempts to bring about rehydration of a calcium silicate hydrate (I) sample by cooling from various temperatures, 6 mm. pressure of water vapour being maintained throughout. Care was taken to ensure that constant weight was attained at each stage; in several cases this took one month or more, as the re-absorption of water was in general very slow. The proportion of the expelled water, that was regained on reaching equilibrium at 20°, decreased as the temperature to which the material had been heated increased, the samples heated to 95°, 230°, and 330° regaining, respectively, 57, 25, and 14% of the expelled water on cooling to 20°. With the first sample increase of the partial vapour pressure to 15 mm. at 20° brought about complete replacement of the expelled water.

(7) *Dehydration and rehydration isotherms for a sample of calcium silicate hydrate* (I). Dehydration isotherms for calcium silicate hydrate (I) might be constructed for any desired temperature from the family of isobars given in Fig. 1. A curve was, however, obtained directly by exposing a single sample to successively lower vapour pressures at room temperature. Subsequently the vapour pressure was raised again, and a rehydration iso-

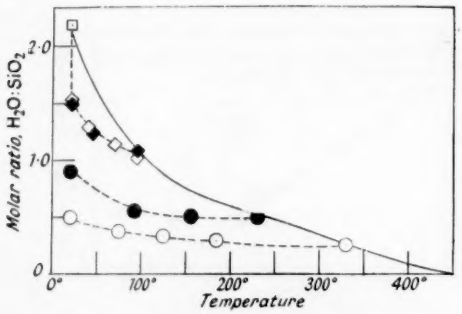


FIG. 4. *Rehydration isobars for calcium silicate hydrate* (I): *Sample* (1), $CaO:SiO_2 = 0·99$.

Full curve:
Dehydration from $H_2O : SiO_2$ 2·07
○ *Rehydration from* 330°
● *Rehydration from* 230°
◇ *Rehydration from* 95°
◆ (*Separate expts.*)
} $p_{H_2O} = 6$ *mm.*
□ *Ditto after standing at* 20° *and* $p_{H_2O} = 155$ *mm.*

therm obtained. The results of two such experiments (see Fig. 5) show, in agreement with those obtained by rehydration of samples heated to 95°, that water in excess of about 1·0 mol. can be replaced by exposure to water vapour at a suitable pressure and temperature. In both cases, however, there is a marked hysteresis effect, and reabsorption of the water is slow. Total periods of 44 and 105 days were occupied in the reabsorption isotherms in experiments I and II respectively, although a considerable proportion of the expelled water was reabsorbed in much shorter times in each case. The dehydration isotherm given in Fig. 5 is of the same general form as that obtained by Bessey (*op. cit.*) for a similar sample. The flat part of the curve occurs at a water content of about 2·0, compared with about 2·5 in Bessey's experiment.

(8) *X-Ray investigation of a fibre of natural riversideite after it had been heated to various temperatures.* As already stated, natural riversideite is a fibrous intergrowth of wilkeite and calcium silicate hydrate (I). A detailed description of this intergrowth, and of the *X*-ray patterns obtained from it, has been given elsewhere (Taylor, *Min. Mag., loc. cit.*). *X*-Ray rotation and zero-layer Weissenberg photographs were taken, about the fibre axis, of a single fibre of riversideite in its natural state and after it had been heated successively to 100°, 250°, 450°, 550°, 700°, 800°, and approximately 1000°. At temperatures up to 450° inclusive, the partial pressure of water vapour was maintained at 6 mm. The photographs all showed reflections corresponding to the presence of a single crystal of wilkeite, with its *c*-axis parallel to the fibre direction, together with preferred orientation patterns of calcium silicate hydrate (I) or its alteration products. The more important features of these preferred orientation patterns, from the standpoint of the present investigation, were as follows:

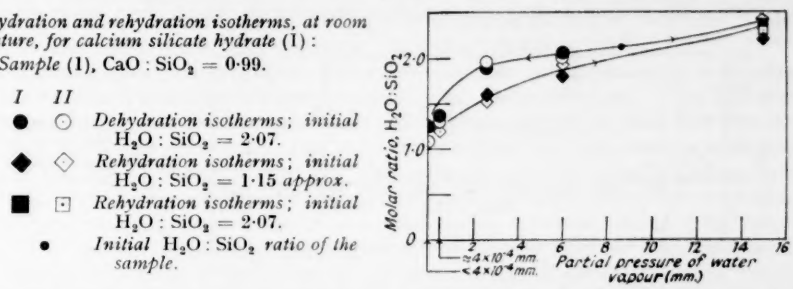
(*a*) In the unheated material, the calcium silicate hydrate (I) crystals are oriented with the mean position of the *b* or 3·65 Å axis parallel to the fibre direction. Two separate 001 reflections were observed, with spacings of 14·0 ± 0·4 Å (strong) and 10·4 ± 0·4 Å (weak). The indexing of these reflections was established with certainty from oscillation photographs about the fibre axis, and from the Weissenberg photographs.

(*b*) The pattern given by the fibre, after it had been heated to 100°, was still essentially that of calcium silicate hydrate (I). The *hk*0 reflections were unchanged in spacings and intensities. However, the 001 spacing of 14 Å had disappeared, whereas that of 10·4 Å had become more intense. Changes in the remaining (*hkl* or 00*l*) reflections were observed; these could be associated with the change in the *c*-axis.

(*c*) After heating to 250°, the pattern given by the fibre was still fundamentally that of calcium silicate hydrate (I). The same *hk*0 reflections were present, but all were slightly reduced in spacing, indicating a decrease in both the *a*- and *b*-axes. The 10·4 Å spacing had been replaced by one of 9·3 ± 0·3 Å. Further changes in the remaining reflections were observed. In a preliminary experiment, a separate fibre was heated to 220°. This showed two 001 reflections, with spacings of 10·4 and 9·3 Å.

(*d*) Heating to 450° or 550° produced no further significant changes in the pattern. At 700°, however, a different preferred orientation pattern was observed. This resembled that of the dehydrated calcium silicate hydrate (I), in having a layer line spacing of about 3·60 Å,

FIG. 5. *Dehydration and rehydration isotherms, at room temperature, for calcium silicate hydrate* (I): *Sample* (I), $CaO : SiO_2 = 0·99$.



and a strong reflection on the first layer at 2·97 Å, but differed from it in other respects, other strong spacings occurring at 10·1 and 3·36 Å, both on the zero layer. The formation of this product was confirmed with another fibre of riversideite.

(*e*) At 800° or 1000°, the pattern was identical with that of β-wollastonite ($CaSiO_3$). This substance also has one axis of length 7·27 (2 × 3·635) Å (Warren and Biscoe, *Z. Krist.*, 1931, **80**, 391) and the photographs showed that it was oriented with this axis parallel to the fibre direction. The wilkeite reflections remained unchanged, even after the fibre had been heated to 1000°, and it is reasonable to conclude that this substance does not interact significantly with calcium silicate hydrate (I) or its dehydration products up to this temperature.

(9) *X-Ray powder investigation of an artificially prepared calcium silicate hydrate* (I), *after heating to various temperatures.* *X*-Ray powder photographs were taken of a laboratory preparation of calcium silicate hydrate (I) (sample 5; lime : silica molar ratio 0·95) after it had been heated to 120°, 240°, 450°, and 1000°. Except at the last temperature, the partial pressure of water vapour was kept at 6 mm. Heating to the first three temperatures left the *X*-ray pattern essentially unaltered, except for a change in the 001 spacing. This was initially 12·3 Å, falling to 10·4 Å at 120° and 9·3 Å at 240° or 450°. All the *hk*0 lines were also slightly decreased in spacing at the last two temperatures, but the change was very small relative to that in the 001 spacing, being in the region of 1—2%. The sample heated to 1000° gave the pattern of β-wollastonite. The sample heated to 120° was rehydrated by standing over water in a vacuum desiccator for 60 days at room temperature. The 001 spacing became diffuse, with a maximum at about 11 Å. This seems to indicate partial but not complete reversal of the lattice shrinkage.

The results of the dehydration experiments thus confirm those given by the natural

riversideite, but are necessarily less detailed. They are also consistent with data of Thilo, Funk, and Wichmann (*loc. cit.*) who, however, did not observe the low-angle reflections.

(10) *Differential thermal analysis curve of calcium silicate hydrate* (I). This was kindly determined by Mr. D. B. Honeyborne (Building Research Station), using the sample mentioned in the previous section. The curve (Fig. 6) shows an endothermic peak at about 100° and a marked exothermic one at about 800°.

Discussion

The Hydration States of Calcium Silicate Hydrate (I).—It is well established that the interpretation of dehydration curves is not straightforward in the case of ill-crystallised substances, unless additional data are available. In the present case, the *X*-ray data, taken in conjunction with the isobars, enable a reasonably certain picture of the hydration states to be obtained. Owing to the sharpness of the effects, the data obtained from the natural riversideite were particularly valuable in this respect.

The riversideite results show that calcium silicate hydrate (I) can exist in a number of definite states of hydration. Of these, the most highly hydrated state so far observed corresponds to the 001 spacing of 14 Å, but its exact water content is not certain. The isobars of the samples prepared at room temperature rise to values of 2·0 or more without tending to a limit. On the other hand, the *X*-ray photographs suggest that the 14-Å hydrate is the predominating one in natural riversideite, which has a water content of about

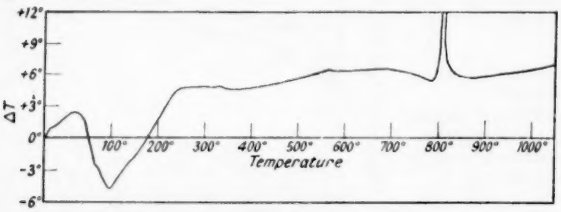


Fig. 6. *Differential thermal analysis curve for calcium silicate hydrate* (I): *Sample* (1), $CaO : SiO_2 = 0{\cdot}99$.

1·4. As will be shown later, the calcium silicate hydrate (I) in riversideite is a mixture of the 14-Å hydrate with one having a water content of 1·0. The water content of the 14-Å hydrate is therefore unlikely to be much above 2·0. It may be 2·5, as supposed by Le Chatelier (*loc. cit.*).

The second state of hydration corresponds to an 001 spacing of 10·4 Å. No point of inflection corresponding to this hydrate is visible in the isobars of the samples prepared at room temperature, but those of the hydrothermal preparation, and of natural riversideite, show points of inflection at water contents of 1·1 and 0·8, respectively. In view of the uncertainties involved, especially in the case of the riversideite, it is reasonable to conclude that this hydrate has a water content of 1·0.

A third state of hydration corresponds to an 001 spacing of 9·3 Å and a water content of 0·5 mol. The point of inflection corresponding to this hydrate is shown, to varying degrees, in the isobars of all the samples studied. Further dehydration yields an anhydrous residue.

The water contents, 001 spacings, and temperatures of formation of the three hydrates can thus be summarised in the following table:

Water content, mols.	*ca.* 2·5	1·0	0·5
001 Spacing, Å	14·0 ± 0·4	10·4 ± 0·4	9·3 ± 0·3
Approx. temp. of formation at ordinary humidities	<20°	100°	250°

Formation of Mixed Hydrates.—On account of its layer structure, calcium silicate hydrate (I) readily forms mixed hydrates. These are of two extreme types. In natural riversideite, both the 14·0 Å and the 10·4 Å state are present; separate 001 spacings, probably corresponding to both *c*-axes, can be distinguished in the *X*-ray photographs. This must indicate that each crystal contains both hydrates, in blocks stacked in a

direction parallel to the *c*-axis, and each containing a sufficient number of unit cells to produce sharp diffraction effects.

The samples prepared at room temperature, on the other hand, give a single 001 spacing at an intermediate value of about 12 Å. The 001 reflection is usually broad, and few if any *hkl* reflections can be detected (Part I, *loc. cit.*). This appears to indicate that layers of both hydrates are present, as in natural riversideite, but that they are mixed together in a more or less random manner.

The differences between the dehydration isobars of riversideite and those of the artificial preparations lend support to these conclusions. In the former, a distinct point of inflection is observed at about 100°, corresponding to the formation of the monohydrate. This can be accounted for if the higher hydrate, which is present at lower temperatures, is in the form of relatively large crystals, which would undergo dehydration at a sharply defined temperature. The absence of this point of inflection in the laboratory samples, on the other hand, may well be explained if the crystals of the higher hydrate are small and variable in size, in the order of a few unit cells. Such crystals would be expected to dehydrate over a wider range of temperature, thereby giving rise to a smooth isobar.

Constitutional Water.—Dehydration from the highest observed state of hydration to the monohydrate reduces the *c*-spacing, but does not affect the *hk*0 reflections. This suggests that water in excess of one molecule is not essential to the structure of the layers, but is present in the form of molecules held loosely between them. This behaviour is closely analogous to that of montmorillonite and other clay minerals (Brindley, " X-Ray Identification and Crystal Structure of Clay Minerals," Min. Soc., London, 1951).

Reduction in the molar water content below 1·0 is usually accompanied by a decrease in the *a* and *b* axes, and a certain tendency to broadening of the *hk*0 lines. It is therefore probable, as Roller and Ervin (*loc. cit.*) and Thilo (*loc. cit.*) have suggested, that this quantity of water is essential to the structure. This may indicate that the compound is built from Ca^{2+} ions and $(H_2SiO_4)^{2-}$ groups. However, the existence of other possibilities, such as $Ca(SiO_3H)(OH)$, implying the existence of metasilicate chains or rings, cannot be overlooked. The fact that the remaining water is lost in two equal stages, at temperatures in the neighbourhood of 170° and 300° respectively, indeed provides some support for this hypothesis.

The Products of Complete Dehydration of Calcium Silicate Hydrate (I).—The results described in sections 8 and 9 indicate that the conversion of calcium silicate hydrate (I) into β-wollastonite does not occur through the intermediate formation of any amorphous phase. The β-wollastonite, formed at 800° or above, is oriented, and all the products that were obtained at lower temperatures contained oriented, crystalline material. A high degree of order thus appears to be maintained throughout the dehydration process.

The *X*-ray patterns of both natural and artificial samples heated to 450° or 550° show that the essential framework of calcium silicate hydrate (I) can exist, though probably in a partly disordered form, after all the water has been driven out. At 700° a rearrangement takes place, giving a hitherto unrecognised phase, and at 800° a further change to β-wollastonite occurs. The *X*-ray patterns of all these compounds show certain marked resemblances, notably in the existence of an axis of approximately 7·3 or 3·65 Å, the orientation of which is unchanged throughout the dehydration process. Close structural resemblances between all of them evidently exist.

The Relation Between Water Content and Molar Lime : Silica Ratio.—The results given in Fig. 2 show that the water content of calcium silicate hydrate (I), expressed as the ratio $H_2O : SiO_2$, is independent of the lime : silica molar ratio for any given conditions of temperature and humidity. This appears to rule out the hypothesis put forward by Le Chatelier (*loc. cit.*), and accepted by many later investigators, that the varying lime : silica ratio can be explained by the adsorption of varying amounts of calcium hydroxide on the surface of a hydrated monocalcium silicate. If this were the case, the adsorbed lime would almost certainly be in the form of hydroxide, and this would cause the water content of the sample to vary with the lime : silica ratio. The adsorbed calcium hydroxide would, furthermore, be expected to decompose in the region of 400°; the isobars show conclusively that this does not occur. The results show that the variation in lime : silica ratio can be described as addition to, or removal from, the structure of the elements of calcium oxide.

This appears to denote the existence of some form of solid solution. More precise understanding of the nature of this must await further information concerning the structure.

Interpretation of the Differential Thermal Analysis Curve.—Comparison of the thermal analysis curve (Fig. 6) with the dehydration isobars of the same sample (Fig. 1) shows that the endothermic peak at about 100° in the former can be attributed to the loss of the interlamellar water. The only other significant feature on the curve is the pronounced exothermic peak at about 800°. This can be attributed to the recrystallisation of the anhydrous residue into wollastonite. This conclusion is in accordance with the results of Thilo, Funk, and Wichmann (*loc. cit.*), who observed that this change took place at 750° and that it was strongly exothermic.

Determination of Calcium Hydroxide in the Presence of Calcium Silicate Hydrate (I).—On account of its importance in relation to the chemistry of Portland cement, numerous methods have been suggested for the quantitative determination of uncombined calcium hydroxide in the presence of hydrated calcium silicates. The majority consisted in the extraction of the uncombined calcium hydroxide with ethylene glycol or similar solvents. It was, however, shown by Bessey (*op. cit.*, p. 285) that such methods were unsatisfactory when applied to hydrated materials. This has been confirmed by the present author (unpublished work).

The close agreement between the observed and the calculated curves in Fig. 2, for the sample of lime : silica molar ratio 1·95, suggests that analysis of the dehydration isobars would provide a more satisfactory method of analysis. This was to some extent envisaged by Bessey (*op. cit.*), who attempted to determine the amount of uncombined calcium hydroxide from the loss in weight between 350° and 550°. The dehydration isobar method can only safely be applied at present in cases where hydrated calcium silicates other than calcium silicate hydrate (I) are known to be absent. The determination of the dehydration isobars of calcium silicate hydrate (II) (Part I, *loc. cit.*), and other related substances, is being undertaken.

Experimental

Determination of Dehydration Isobars.—100—400 Mg. of the substance were placed in a glass weighing tube, which, with its stopper, was placed in a stainless-steel boat. This was inserted into a horizontally mounted glass tube 2·5 cm. in diameter, of which one end was stoppered, and the other sealed off and placed within an electric furnace. This could be operated up to 520°, the temperature being measured by means of a chromel–alumel thermocouple. The tube carried two side arms. One of these led to a flask containing a saturated solution, or in some cases a mixture of two solid phases, and immersed in a thermostat at 21°; this maintained a constant partial pressure of water vapour in the apparatus. The other, bearing a tap, enabled the apparatus to be evacuated to a nominal pressure of about 10 mm. as read on a miniature McLeod (Edwards's " Vacustat ") gauge, in order to accelerate the attainment of equilibrium.

In operation, the furnace was raised to successively higher temperatures, commencing at room temperature. The tube and its contents were cooled over phosphoric oxide after each period of heating, and weighed, according to a standardised procedure. The times needed to reach equilibrium at each successive temperature varied between a few hours and 2—3 days, depending chiefly on the temperature and the increment in the temperature. In all doubtful cases, a series of weighings was made at the same temperature, and the loss in weight plotted against the time, in order to establish whether equilibrium was being attained. A complete run on a single sample, ending at the maximum temperature of 520°, usually occupied 7—14 days.

Owing to the virtual impossibility of preparing samples of calcium silicate hydrate (I) free from calcite, and the ready reaction of the substance towards atmospheric carbon dioxide, certain precautions were necessary in order to avoid errors in the assumed composition, arising from uncertainty in the amount of the dioxide present. The most satisfactory procedure was to continue the isobar to 450° or above, at which temperatures all the water is driven off. The residue was transferred to a platinum crucible and ignited; the loss in weight gave the amount of carbon dioxide present in the sample actually used for determining the isobar. In cases where the isobar was terminated at a lower temperature, this method was inapplicable, and the carbon dioxide content and ignition loss were determined on separate portions.

The solutions and mixtures used for maintaining constant partial pressures of water vapour

were as follows: saturated $(NH_4)_2SO_4$, $p_{H_2O} = 15$ mm., saturated $CaCl_2.6H_2O$, $p_{H_2O} = 6$ mm., and saturated $LiCl,H_2O$, $p_{H_2O} = 2{\cdot}8$ mm. (data from O'Brien, *J. Sci. Instr.*, **1948**, **25**, 73), and $Mg(ClO_4)_2.2H_2O + Mg(ClO_4)_2.4H_2O$, $p_{H_2O} \approx 4 \times 10^{-4}$ mm., and $Mg(ClO_4)_2 + Mg(ClO_4)_2.2H_2O$, $p_{H_2O} < 4 \times 10^{-4}$ mm. (data of Powers and Brownyard, *J. Amer. Concrete Inst.*, **1947**, **43**, 249). Phosphoric oxide was also used, and appeared to maintain a vapour pressure similar to that of anhydrous magnesium perchlorate; but the attainment of equilibrium was found to be very slow, probably as a result of the formation of a surface film on the oxide, and its use was therefore abandoned.

The thermostat was operated at as little as possible above room temperature, in order to avoid the danger of water condensing on those parts of the apparatus which were at room temperature, when saturated ammonium sulphate was being used, and thereby introducing doubt regarding the vapour pressure within the apparatus.

The procedure described above was used also in the rehydration experiments (Fig. 4). The times taken for reaching apparent equilibrium at each temperature were, as already mentioned, very much greater than in the dehydration experiments. It is therefore unlikely that any serious error can have been introduced into any of the present results by changes in weight occurring between removal of the substance from the furnace and weighing.

Determination of Isotherms.—The isotherms shown in Fig. 5 were obtained by measurement of the changes in weight of samples contained in porcelain crucibles placed in vacuum-desiccators at room temperature. The same reagents were used for maintaining given partial pressures of water vapour as in the isobaric experiments.

Differential Thermal Analysis.—The result given in Fig. 6 was determined for a heating rate of 10°/min. The reference material was fused kaolinite and the mass of sample used was 0·21 g.

X-Ray Apparatus.—The Unicam 6-cm. diameter single-crystal camera and a 5·73-cm. diameter Weissenberg camera were used with a sealed *X*-ray tube giving copper radiation. A nickel-foil filter was placed in contact with the film. The single-crystal camera was also used for the powder work.

Materials.—The calcium silicate hydrate (I) samples were prepared by methods already described in Parts I and II (*locc. cit.*). Analytical data, expressed as percentage composition and molar lime : silica ratio, are as follows:

CaO, %	SiO_2, %	H_2O, %	$CaCO_3$, %	CaO/SiO_2
(*a*) Samples prepared from $Ca(OH)_2$ and SiO_2 gel.				
(1) 35·7	38·5	24·0	1·7	0·99
(2) 42·0	34·7	22·1	1·2	1·30
(*b*) Samples prepared by double decomposition.				
(3) 19·2	21·3	58·6	0·8	0·91
(4) 32·3	36·8	27·2	3·6	0·94
(5) 33·3	37·6	25·5	3·6	0·95
(6) 37·1	32·2	27·3	3·4	1·24
(7) 42·4	23·3	20·1	14·5	1·95

CaO, %	SiO_2, %	H_2O, %	$CaCO_3$, %	CaO/SiO_2
(*c*) Samples prepared from $Ca_3Si_2O_7$.				
(8) 30·2	36·3	22·1	11·4	0·89
(9) 35·7	27·9	25·6	10·9	1·37
(*d*) Sample prepared hydrothermally.*				
(10) 37·2	42·6	14·1	6·1	0·94
(*e*) Natural riversideite.†				
(11) 17·7	21·5	8·8	—	0·9

* This was sample 67 of Part II (*loc. cit.*).

† This is a very approximate result obtained (Taylor, *Min. Mag.*, *loc. cit.*) by correcting the actual analysis for the presence of wilkeite, diopside, idocrase, and calcite.

The analysis of the calcium hydroxide sample was given in Part II (*loc. cit.*).

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21 Torrington Square, London, W.C.1. [*Received, August 6th*, 1952.]

34. *The Constitution of Products formed from o-Phenylenediamines and Alloxan in Neutral Solution. Part II.* Rudy and Cramer's "bis-Barbiturylidene Ether."*

By F. E. King and J. W. Clark-Lewis.

The compound previously described as "bis-[5-(1-methyl-2 : 3-dihydrobenzimidazolyl-3)barbituryl-5] ether" (Rudy and Cramer, *Ber.*, 1939, **72**, 227, 728) is shown to be the anhydride of 1 : 2 : 3 : 4-tetrahydro-3-hydroxy-4-methylquinoxaline-2-*spiro*-5'-(hexahydro-2' : 4' : 6'-triketopyrimidine). Similarly, a *pseudo*-base structure, *viz.*, 6 : 7-dichloro-1 : 2 : 3 : 4-tetrahydro-3-hydroxy-4-methylquinoxaline-2-*spiro*-5'-(hexahydro-2' : 4' : 6'-triketopyrimidine), or its anhydride, may be attributed to a previously unidentified product obtained from alloxan and 4 : 5-dichloro-2-dimethylaminoaniline (Barlow, *J.*, 1951, 2226; Barlow, Ing, and Lewis, *ibid.*, p. 3142).

By the action of acetic anhydride on certain quinoxaline-2-carboxyureides, quinoxaline-2-carboxyacetamides are obtained.

It has recently been proved (King and Clark-Lewis, *J.*, 1951, 3080) that the initial condensation product of alloxan with *o*-dimethylaminoaniline is not the anil (I), as supposed by Rudy and Cramer (*Ber.*, 1938, **71**, 1234; 1939, **72**, 227, 728), but the spiran (II; R = H) formed in a unique ring-closure involving an *N*-methyl group. Accompanying the spiran is a sparingly-soluble by-product described by Rudy and Cramer as a "bis-barbiturylidene ether" and believed by them to have the constitution (III). Since the so-called ether can also be prepared merely by the action of molecular oxygen or of alloxan on the primary condensation product, the two compounds are presumably in close structural relationship and it is therefore difficult, with the adoption of the revised expression (II; R = H), to accept the formula (III). On the other hand, oxidation under the specified mild conditions is readily explicable in terms of the spiran structure (II), and further investigation has shown that the supposed ether is the anhydride (IV) of a carbinol-amine (V; R = H) similar in structure to the initial spiran (II; R = H).

The light absorption of the colourless carbinol-amine (V; R = H), which is quite different from that of the yellow spiran (II; R = H) or of the quinoxalinecarboxyureides (King and Clark-Lewis, *J.*, 1951, 3379), resembles the absorption of a product $C_{12}H_{12}O_4N_4Cl_2$ obtained from alloxan and 4 : 5-dichloro-2-dimethylaminoaniline (Barlow, *J.*, 1951, 2226). The dichloro-compound shows a bathochromic shift of about 20 mμ in the position of two subsidiary maxima, but the similarity in light absorption and in the method of preparation clearly favours the analogous structure (V; R = Cl) and this has been confirmed by catalytic dechlorination to (V; R = H). The expression (V; R = Cl) implies an empirical formula $C_{12}H_{10}O_4N_4Cl_2$, which is in better agreement with the reported analytical figures than is the constitution $C_{12}H_{12}O_4N_4Cl_2$ (Barlow, *loc. cit.*; Barlow, Ing, and Lewis, *J.*, 1951, 3242).

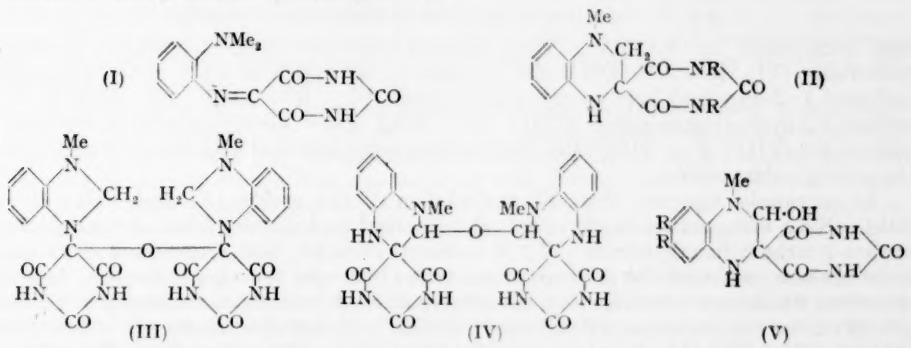
The carbinol-amine (V; R = H) crystallises as a monohydrate, and analyses and a molecular-weight determination by *X*-ray diffraction are in agreement with the molecular formula $C_{12}H_{12}O_4N_4,H_2O$ but the possibility, although remote, that the compound is the anhydride trihydrate cannot be entirely excluded since attempts to obtain the anhydrous base invariably result in the formation of the dimeric anhydride, $C_{24}H_{22}O_7N_8$ (IV). The low solubility of the compound affects the reliability of molecular-weight determinations and the published values (Rudy and Cramer, *loc. cit.*) are discordant and inaccurate. The carbinol-amine $C_{12}H_{10}O_4N_4Cl_2$ which is not solvated similarly yields an anhydride, $C_{24}H_{18}O_7N_8Cl_4$.

The formation of the carbinol-amine (V; R = H) by oxidation with molecular oxygen is comparable with the preparation from strychnine of *pseudo*strychnine (Leuchs, *Ber.*, 1937, **70**, 1543). Proof of the constitution (V; R = H) has been obtained by alkaline hydrolysis which affords 3 : 4-dihydro-3-keto-4-methylquinoxaline-2-carboxylic acid and formic acid. The liberation of formic acid, which also occurs with the dichloro-compound (V; R = Cl), results from the instability of the β-aldehydo-dicarboxylic acid generated on

* Part I, *J.*, 1951, 3379.

hydrolysis of the quinoxaline ring; with the loss of the formyl group, recyclisation and atmospheric oxidation follow, giving the quinoxalinecarboxylic acid.

Salts of the carbinol-amine (V; R = H) are almost completely hydrolysed in water but a hydrogen sulphate of the corresponding anhydro-base was prepared by dissolving the amine in sulphuric acid and then diluting with ethanol. Both carbinol-amines (V; R = H and R = Cl) are resistant to acid hydrolysis, and this provides further evidence against the dihydrobenziminazole structure (III), which, viewed as a diaza-acetal, would be expected to yield formaldehyde under acid conditions. It also indicates that the barbiturate ring is intact in these amines since the ureide side-chain of quinoxaline-2-carboxyureides is readily cleaved by acids (Part I).



Vigorous oxidation of (V; R = H) with hydrogen peroxide in acetic acid yields 1-methylbenziminazole as the final product. Formation of the latter was considered by Rudy and Cramer to be evidence for the dihydrobenziminazole nuclei postulated in their structure (III), but as the compound (II; R = H) behaves similarly under these conditions it is clear that the 1-methylbenziminazole is produced by secondary reactions. Both carbinol-amines failed to give ethers with the simple alcohols, but this may be attributed to their very low solubility in these solvents.

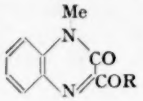
Oxidation of the *NN*-dimethyl derivative (II; R = Me) with molecular oxygen likewise gave a compound resembling the other carbinol-amines, and which from its analysis is either the carbinol-amine hemihydrate, $C_{14}H_{16}O_4N_4,\frac{1}{2}H_2O$, or an ether dihydrate, $C_{28}H_{30}O_7N_8,2H_2O$. 1 : 2 : 3 : 4 : 2′ : 4′-Hexahydro-2′ : 4′-diketo-4 : 3′-dimethylglyoxalino-(1′ : 5′-1 : 2)quinoxaline (*J.*, 1951, 3081, formula III), on the other hand, did not form a carbinol-amine but was oxidised to the orange 2 : 3-dehydro-derivative (*loc. cit.*, formula VII).

It has been observed that in the preparation of the 6 : 7-dichloro-carbinol-base with acetic acid as solvent, a highly coloured by-product is obtained (Barlow, *loc. cit.*); this has now been identified as 6 : 7-dichloro-9-methyl*iso*alloxazine. These two compounds were also formed in aqueous ethanol, but in neither experiment was any of the dichloro-analogue of (II; R = H) detected, apparently because of its great ease of oxidation. The work of Rudy and Cramer (*loc. cit.*) affords other examples, in the 6 : 7-dimethyl series, of this ready oxidation.

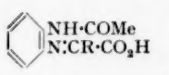
As precautions were taken to eliminate secondary amine, it is unlikely that the formation of 6 : 7-dichloro-9-methyl*iso*alloxazine arose from the presence of this impurity; moreover, alloxan and primary-secondary *o*-diamines in neutral solution afford 3-keto-3 : 4-dihydro-4-alkyl(or -aryl)quinoxaline-2-carboxyureides (Part I). Rudy and Cramer have reported the formation of an *iso*alloxazine from the bis-barbiturylidene ether (III) by boiling sodium carbonate solution, and it presumably occurs through hydrolysis to a 5-(*o*-methylaminophenylamino)barbituric acid followed by cyclisation to the corresponding dihydro*iso*alloxazine which is then oxidized, *e.g.*, by air. The 6 : 7-dichloro-9-methyl*iso*alloxazine isolated in the present work, therefore, is probably a secondary product derived from the carbinol-amine (V; R = Cl).

Acetolysis of Quinoxaline-2-carboxyureides.—Condensation of *N*-methyl-*o*-phenylene diamine with alloxan in neutral solution yields 3 : 4-dihydro-3-keto-4-methylquinoxaline-2-

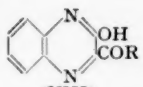
carboxyureide (VI; R = NH·CO·NH_2) (see Part I), erroneously supposed by Kühling and Kaselitz (*Ber.*, 1906, **39**, 1314) to be an anil. According to these authors the "anil" yields an acetyl derivative, which was represented as (VII) (cf. Barlow, Ing, and Lewis, *J.*, 1951, 3242). We have investigated the action of acetic anhydride on (VI; R = NH·CO·NH_2) and also on the hydroxyquinoxaline-carboxyureide (VIII; R = NH·CO·NH_2). Acetolysis occurred in each case, and the structure of the products (VI and VIII; R = NH·COMe) has



(VI)



(VII; R = ·NH·CO·NH_2)



(VIII)

been established by synthesis. Thus 3-acetylcarbamyl-1 : 2-dihydro-2-keto-1-methylquinoxaline (VI; R = NH·COMe) was obtained by the action of acetic anhydride on 3-carbamyl-1 : 2-dihydro-2-keto-1-methylquinoxaline (VI; R = NH_2), and similarly 3-carbamyl-2-hydroxyquinoxaline (VIII; R = NH_2) gave 3-acetylcarbamyl-2-hydroxyquinoxaline (VIII; R = NH·COMe), the products being identical with those derived from the corresponding ureides.

As previously reported (Part I), methylation of the ureides (VI and VIII; R = NH·CO·NH_2) with methyl iodide affords the identical 3 : 4-dihydro-3-keto-4-methylquinoxaline-2-carboxydimethylureide (VI; R = dimethylureido), and Zerewitinoff determination has now confirmed the presence of one active hydrogen atom per molecule. Among structures which may be written for a dimethylureide side chain, those containing methoxyl groups can be eliminated since Zeisel determination gave negative results and it is known that compounds of this type containing methoxyl groups readily yield methyl halides (Curd, Davy, and Richardson, *J.*, 1949, 1732, and references quoted there). Two possibilities remain, *viz.*, –CO·NMe·CO·NHMe and –CO·NH·CO·NMe_2. The quinoxaline-carboxydimethylureide (VI; R = dimethylureido) and its 4-phenyl analogue have now been found to be inert towards acetic anhydride under conditions which cause cleavage of the –CO·NH·CO– group in the unmethylated ureides. It seems probable, therefore, that the grouping –CO·NH·CO– is not present in the dimethylureides (VI), which accordingly must have the alternative side-chain R = NMe·CO·NHMe.

The ultra-violet spectra of (VIII and VI; R = NH·CO·NH_2) in neutral solution are indistinguishable, but differ from that of 3-methoxyquinoxaline-2-carboxyureide, so that the compound represented as (VIII; R = NH·CO·NH_2) is probably the alternative 3 : 4-dihydro-3-keto-quinoxaline-2-carboxyureide, *i.e.*, (VI; R = NH·CO·NH_2, with NH for NMe). The predominance of the lactam over the lactim form has been established in several other heterocyclic systems recently investigated (Marshall and Walker, *J.*, 1951, 1004; Hearn, Morton, and Simpson, *ibid.*, p. 3318, 3329).

Experimental

1 : 2 : 3 : 4-*Tetrahydro*-3-*hydroxy*-4-*methylquinoxaline*-2-spiro-5′-(*hexahydro*-2′ : 4′ : 6′-*triketopyrimidine*) (V; R = H).—(*a*) Alloxan hydrate (40 g., 1·3 mol.), dissolved in water (60 c.c.), was added to a mixture of *o*-dimethylaminoaniline (26·2 g., 1 mol.), ethanol (250 c.c.), and 10N-hydrochloric acid (10 drops), and the solution was kept at room temperature. Filtration after 3 days yielded a mixture from which the yellow spiran (II; R = H) was extracted with pyridine as previously described (*J.*, 1951, 3080; Rudy and Cramer, *loc. cit.*). A solution of the residue (8 g., 15%) in boiling water (charcoal) slowly deposited **1 : 2 : 3 : 4-*tetrahydro*-3-*hydroxy*-4-*methylquinoxaline*-2-spiro-5′-(*hexahydro*-2′ : 4′ : 6′-*triketopyrimidine*) *monohydrate*** (6 g., 11%) in colourless needles or prisms, m. p. from 370—375° (decomp.) [Found: C, 48·7; H, 5·0; N, 18·4; NMe, 7·0%; *M* (by *X*-ray diffraction), 1204/*n* (determination by Dr. S. C. Wallwork). $C_{13}H_{12}O_4N_4,H_2O$ requires C, 49·0; H, 4·8; N, 19·0; NMe, 9·9%; *M*, 294·2]. Light absorption in H_2O (and in N-HCl): max. at 250 (ε = 22,800), 270 (ε = 8750), and 277 (ε = 7430); min. at 227 mμ (ε = 9250), 268 (ε = 8500), and 274 mμ (ε = 6840).

(*b*) A slow stream of oxygen was passed through a suspension of the spiran (II; R = H) (1·5 g.) in boiling water (50 c.c.). The yellow solid dissolved during 3—4 hours, and the cold solution deposited the carbinol-base (V; R = H) (0·9 g., 55%) identical with that obtained by method (*a*) (cf. Rudy and Cramer, *loc. cit.*).

(*c*) The dichloro-compound (V; R = Cl) (1 g.), sodium acetate (1 g., 2·7 mol.), sodium hydrogen carbonate (0·5 g., 2·05 mol.), Raney nickel, and water (60 c.c.) were shaken with hydrogen at 100° ± 10°/120 atm. for 10 hours. The catalyst was removed by filtration (kieselguhr) and washed with hot water, and the combined filtrate was concentrated to 50 c.c. Crystallisation of the deposited solid afforded the hydrated carbinol (II; R = H) (0·239 g., 29%), m. p. and mixed m. p. 372—374° (decomp.). The carbinol does not give the violet colour with hydrogen peroxide–hydrochloric acid characteristic of the spiran (II; R = H). When dried at 160° *in vacuo* for 1 hour or to constant weight at 100—120°, the carbinol-amine hydrate is converted into *di*[(*barbituric acid*)-5-spiro-2′-(1′ : 2′ : 3′ : 4′-*tetrahydro*-4′-*methylquinoxalin*-3′-*yl*)] *ether* (IV), m. p. from 370—375° (decomp.) (Found: C, 54·1; H, 4·6; N, 21·4. $C_{24}H_{22}O_7N_8$ requires C, 53·9; H, 4·2; N, 21·0%).

A solution of the carbinol hydrate (1 g.) in concentrated sulphuric acid (5 c.c.) was poured into ethanol. The precipitate (*ca.* 0·5 g.) was collected after 24 hours, and washing with ethanol gave the *quinoxalinium hydrogen sulphate*, decomp. 254° (Found: C, 40·8; H, 3·8; S, 8·2. $C_{12}H_{11}O_3N_4,HSO_4$ requires C, 40·4; H, 3·4; S, 9·0%).

Hydrolysis of 1 : 2 : 3 : 4-*Tetrahydro*-3-*hydroxy*-4-*methylquinoxaline*-2-spiro-5′-(*hexahydro*-2′ : 4′ : 6′-*triketopyrimidine*) (V; R = H).—(*a*) The carbinol-amine (1·25 g.) was boiled with 5N-sodium hydroxide (25 c.c.) until evolution of ammonia ceased. After acidification with 10N-hydrochloric acid the solution was extracted with chloroform from which was isolated 3 : 4-dihydro-3-keto-4-methylquinoxaline-2-carboxylic acid (0·35 g., 38%), crystallising from water in needles, m. p. 170° (decomp.) alone or with an authentic specimen (m. p. and mixed m. p. of the methyl ester, 125°).

(*b*) The carbinol-amine (V; R = H) (1 g.) was hydrolysed as described in (*a*), and the solution acidified with 2N-sulphuric acid. The quinoxaline-carboxylic acid was collected after 24 hours and the filtrate concentrated, the distillation being continued after addition of water (20 c.c.). After titration with 0·1N-sodium hydroxide (32·3 c.c.; 1 mol. of formic acid requires 34·0 c.c.), the resulting sodium salt gave *NN*′-di-*p*-tolylformamidine, m. p. 140—141°, not depressed by admixture with a genuine specimen (Whalley, *J.*, 1948, 1014).

The carbinol-base was not affected by boiling with 2N-hydrochloric acid (3 hours) or ethanolic hydrogen chloride (5%) (8 hours).

1 : 2 : 3 : 4-*Tetrahydro*-3-*hydroxy*-4-*methylquinoxaline*-2-spiro-5′-(*hexahydro*-2′ : 4′ : 6′-*triketo*-1′ : 3′-*dimethylpyrimidine*).—To 1 : 2 : 3 : 4-tetrahydro-4-methylquinoxaline-2-*spiro*-5′-(hexahydro-2′ : 4′ : 6′-triketo-1′ : 3′-dimethylpyrimidine) (II; R = Me) (0·53 g.) (*J.*, 1951, 3080), dissolved in acetic acid (10 c.c.), water (20 c.c.) was added and oxygen was passed through the boiling solution for 5 hours. Evaporation left a residue which crystallised from 2N-hydrochloric. acid, affording 1 : 2 : 3 : 4-*tetrahydro*-3-*hydroxy*-4-*methylquinoxaline*-2-spiro-5′-(*hexahydro*-2′ : 4′ : 6′-*triketo*-1′ : 3′-*dimethylpyrimidine*) as prisms, m. p. 306—307° (Found: C, 54·1; H, 5·03; N, 18·0. $C_{14}H_{16}O_4N_4,\frac{1}{2}H_2O$ requires C, 53·7; H, 5·47; N, 17·9%). Light absorption in H_2O: max. at 253 (ε = 21,800) and 272 (ε = 7500); min. at 227—228 mμ (ε = 9000) (Found: loss at 110° *in vac.*, 5·0. Formation of $C_{28}H_{30}O_7N_8$ requires loss, 5·8%).

Oxidation of 1 : 2 : 3 : 4-*Tetrahydro*-3-*hydroxy*-4-*methylquinoxaline*-2-spiro-5′-(*hexahydro*-2′ : 4′ : 6′-*triketopyrimidine*) (V; R = H).—Hydrogen peroxide (15%; 3·3 c.c.) was added to aqueous acetic acid (50%; 20 c.c.) containing the carbinol-amine (V; R = H) (3 g.), and the solution evaporated to dryness after 1 hour's boiling. The residue was heated on a steam-bath for 5 hours, than basified with 2N-sodium hydroxide, and the whole extracted with ether. Distillation gave 1-methylbenziminazole (0·6 g., 45%), m. p. 58°, characterised by the picrate, m. p. 247° (decomp.) (Found: C, 47·2; H, 2·9; N, 19·7. Calc. for $C_8H_8N_2,C_6H_3O_7N_3$: C, 46·6; H, 3·1; N, 19·4%), and *picrolonate*, decomp. 254° (Found: C, 54·5; H, 3·9; N, 21·4. $C_8H_8N_2,C_{10}H_8O_5N_4$ requires C, 54·6; H, 4·1; N, 21·2%). M. p.s with specimens prepared from authentic 1-methylbenziminazole were not depressed.

Oxidation of 1 : 2 : 3 : 4-*Tetrahydro*-4-*methylquinoxaline*-2-spiro-5′-(*hexahydro*-2′ : 4′ : 6′-*triketopyrimidine*) (II; R = H).—A solution of the spiran (II; R = H) (1 g.) in acetic acid (50%, 40 c.c.) was boiled for 1 hour with hydrogen peroxide (15%, 1 c.c.). 1-Methylbenziminazole (0·25 g., 50%) was isolated and identified as described under (*a*).

4 : 5-*Dichloro*-NN-*dimethyl*-2-*nitroaniline*.—(*a*) 1 : 2 : 4-Trichlorobenzene (100 g.) was slowly poured into nitric acid (*d* 1·5; 300 c.c.), the solution being kept in cold water for 20 minutes. 1 : 2 : 4-Trichloro-5-nitrobenzene, obtained by pouring the solution on ice, crystallised from methanol in needles, m. p. 55—56° (77 g., 61%; cf. Barlow and Ing, *J.*, 1950, 713). A solution of 1 : 2 : 4-trichloro-5-nitrobenzene (52 g., 1 mol.) and dimethylamine (10·3 g., 1 mol.) in ethanol (250 c.c.) was heated in a closed container at 100° for 24 hours. After removal of the solvent,

the residue was extracted with 10N-hydrochloric acid to separate the product from trichloronitrobenzene (25·2 g., 49%). Diluting the acid solution to 2 l. gave **4 : 5-*dichloro*-NN-*dimethyl*-2-*nitroaniline*** (20·3 g., 38%; m. p. 82—91°), which separated from light petroleum as orange prisms, m. p. 99—100° (Found: C, 41·2; H, 3·1; N, 11·9%. $C_8H_8O_2N_2Cl_2$ requires C, 40·9; H, 3·4; N, 11·9%). The light petroleum filtrate deposited an isomer (0·7 g.), probably **2 : 5-*dichloro*-NN-*dimethyl*-4-*nitroaniline***, which crystallised in lemon-yellow plates, m. p. 106—107° (Found: C, 41·2; H, 3·5; N, 12·1%). After filtration from the dichloronitro-amines the diluted aqueous solution was extracted with chloroform, to yield a further product (*ca.* 6%), probably **1-*chloro*-2 : 4-*bisdimethylamino*-5-*nitrobenzene***, which crystallised from light petroleum in yellow prisms, m. p. 87—88° (Found: C, 49·8; H, 6·1; N, 17·5. $C_{10}H_{14}O_2N_3Cl$ requires C, 49·3; H, 5·8; N, 17·2%).

(*b*) Heating **1 : 2 : 4-trichloro-5-nitrobenzene** (34·2 g.) with dimethylamine in pyridine as described for the preparation of *NN*-dimethyl-*o*-nitroaniline by Campbell (*J. Amer. Chem. Soc.*, 1949, **71**, 740) yielded, after removal of pyridine by distillation, a mixture of bases (34 g.) which was separated as under (*a*) into **4 : 5-dichloro-*NN*-dimethyl-2-nitroaniline** (18·1 g., 51%, after crystallisation) and **1-chloro-2 : 4-bisdimethylamino-5-nitrobenzene** (7·6 g., 21%). This method is more convenient in manipulation than (*a*).

4 : 5-Dichloro-*NN*-dimethyl-2-nitroaniline was treated with toluene-*p*-sulphonyl chloride in pyridine; the product was indistinguishable from the original nitro-amine (m. p. 99—100°) and no toluene-*p*-sulphonanilide was isolated.

4 : 5-*Dichloro*-2-*dimethylaminoaniline*.—**4 : 5-Dichloro-2-nitrodimethylaniline** (40 g.) in ethanol (100 c.c.) was reduced with hydrogen at 6 atm. over Raney nickel in 3 hours at room temperature. The catalyst was removed by filtration (kieselguhr), and evaporation gave **4 : 5-*dichloro*-2-*dimethylaminoaniline*** (32 g., 92%), b. p. 174—178°/20 mm., n_D^{19} 1·5982, as a colourless oil darkening rapidly in air (Found: C, 46·8; H, 4·8; N, 13·3. $C_8H_{10}N_2Cl_2$ requires C, 46·9; H, 4·9; N, 13·7%). After treatment with toluene-*p*-sulphonyl chloride, the nitro-amine gave **4 : 5-dichloro-2-dimethylaminoaniline**, b. p. 166—170°/17 mm., n_D^{25} 1·5985, d^{20} 1·2864, R_D 54·45 (Calc.: R_D 54·71). The ***picrate*** crystallised from ethanol in yellow prisms, m. p. 179° (Found: C, 39·1; H, 3·1; N, 16·2. $C_8H_{10}N_2Cl_2,C_6H_3O_7N_3$ requires C, 38·7; H, 3·0; N, 16·1%).

6 : 7-*Dichloro*-1 : 2 : 3 : 4-*tetrahydro*-3-*hydroxy*-4-*methylquinoxaline*-2-spiro-5′-(*hexahydro*-2′ : 4′ : 6′-*triketopyrimidine*) (V; R = Cl).—Alloxan hydrate (35 g.), dissolved in water (50 c.c.) containing concentrated hydrochloric acid (5 drops), was added to a solution of **4 : 5-dichloro-2-dimethylaminoaniline** (25 g.) in ethanol (250 c.c.). The crystalline product (22·5 g.) was collected after 2 days at room temperature, and further quantities (16 and 5·9 g.) were obtained after 6 and 28 days respectively. The solid, which was insoluble in pyridine, was extracted with boiling acetic acid, leaving the crude *iso*alloxazine (below). The product from the cold solution, after 2 further crystallisations from acetic acid (*ca.* 50 c.c./g.), gave **3 : 7-*dichloro*-1 : 2 : 3 : 4-*tetrahydro*-3-*hydroxy*-4-*methylquinoxaline*-2-spiro-5′-(*hexahydro*-2′ : 4′ : 6′-*triketopyrimidine*)** (17 g., 40%) as a felted mat of needles, m. p. 400° (decomp.) (Found: N, 13·6; Cl, 17·3; NMe, 7·4. $C_{12}H_{10}O_4N_4Cl_2,CH_3{\cdot}CO_2H$ requires N, 13·8; Cl, 17·5; NMe, 7·2; loss, 14·8. Found, after drying at 110°: C, 41·5; H, 3·1; N, 16·1; Cl, 20·6; loss, 15·9. $C_{12}H_{10}O_4N_4Cl_2$ requires C, 41·8; H, 2·9; N, 16·2; Cl, 20·6; loss, 14·8%). By more prolonged drying (3 hours at 110°) the carbinol is converted into the anhydride, *di*[(*barbituric acid*)-5-spiro-2′-(6′ : 7′-*dichloro*-1′ : 2′ : 3′ : 4′-*tetrahydro*-4′-*methylquinoxalin*-3′-*yl*)] *ether*, m. p. 400° (decomp.) (Found: C, 42·6; H, 3·0; N, 16·6. $C_{24}H_{18}O_7N_8Cl_4$ requires C, 42·9; H, 2·7; N, 16·7%). The ether was also obtained as rectangular plates, m. p. 400° (decomp.), by boiling the carbinol (V; R = Cl) with nitromethane for 5 minutes (Found: C, 43·7; H, 2·7; Cl, 22·0. Calc. for $C_{24}H_{18}O_7N_8Cl_4$: C, 42·9; H, 2·7; Cl, 21·1%). Ultra-violet light absorption of the carbinol-amine in H_2O: max. at 208 (ε = 30,000), 249 (ε = 18,650), 288 (ε = 6730), and 297 mμ (ε = 6360); min. at 233 (ε = 13,000), 272 (ε = 4010), and 293 mμ (ε = 5720). Comparison of m. p. and ultra-violet light absorption with those of a sample kindly provided by Dr. R. B. Barlow (*loc. cit.*) showed their identity. The carbinol-amine was boiled with 5N-sodium hydroxide for 3 hours, and formic acid identified as in the case of (V; R = H) by conversion into *NN′*-di-*p*-tolylformamidine, m. p. and mixed m. p. 140—141°. The carbinol-amine yields colourless solutions in hot acetic acid and in hot water; it is almost insoluble in the usual organic solvents.

Crystallisation of the reaction product less soluble in acetic acid afforded **6 : 7-*dichloro*-9-*methylisoalloxazine*** (*ca.* 2·5 g., 7%), m. p. 346° (decomp.) (Found: C, 44·6; H, 2·1; N, 19·0. $C_{11}H_6O_2N_4Cl_2$ requires C, 44·5; H, 2·0; N, 18·9%). Light absorption in 95% EtOH: max. at 224 (ε = 27,700), 272 (ε = 32,000), 336 (ε = 6540), and 451 mμ (ε = 9410); min. at 240 (ε = 10,200), 302 (ε = 2840), and 376 mμ (ε = 1950).

Oxidation of 1 : 2 : 3 : 4 : 2′ : 4′-*Hexahydro*-2′ : 4′-*diketo*-4 : 3′-*dimethylglyoxalino*(1′ : 5′-1 : 2)-*quinoxaline*.—Oxygen was passed through a boiling solution of the hydantoin (0·85 g.) in acetic acid (10 c.c.) for 1 hour. The solution rapidly developed a dark orange colour, and evaporation to dryness and washing (alcohol) left an orange solid (0·8 g.), m. p. *ca.* 240°. Fractional crystallisation from alcohol and aqueous alcohol removed a small quantity of impure hexahydro-compound (m. p. 146—148°), giving 1 : 4 : 2′ : 4′-tetrahydro-2′ : 4′-diketo-4 : 3′-dimethylglyoxalino(1′ : 5′-1 : 2)quinoxaline, m. p. 256°, not depressed by the authentic material, m. p. 260° (*J.*, 1951, 3080). Similarly the light absorptions of both specimens in alcoholic solution were identical: light absorption of an 8·77 × 10^{-5} M-solution in 95% EtOH: max. at 218 (ε = 15,650), 225—226 (ε = 15,230), 266 (ε = 12,700), 281·5 (ε = 12,500), 343 (ε = 5470), and 437 mμ (ε = 6390); min. at 216 (ε = 14,850), 224 (ε = 15,100), 245 (ε = 8220), 278 (ε = 12,080), 307 (ε = 1700), and 365 mμ (ε = 1280). The extinction coefficients decreased with dilution, presumably owing to a diminished association of the molecules.

3-*Acetylcarbamyl*-1 : 2-*dihydro*-2-*keto*-1-*methylquinoxaline* (VI; R = NH·COMe).—(*a*) 3 : 4-Dihydro-3-keto-4-methylquinoxaline-2-carboxyureide (VI; R = NH·CO·NH_2) (3 g.) was boiled with acetic anhydride (50 c.c.) for 3½ hours, *i.e.*, 1 hour after solution was complete. A product (2 g., 66%) separated in the cold as yellow needles, m. p. 190°; recrystallisation from ethanol gave 3-*acetylcarbamyl*-1 : 2-*dihydro*-2-*keto*-1-*methylquinoxaline* in yellow needles, m. p. 222° (Found: C, 58·7; H, 4·6; N, 17·2. $C_{12}H_{11}O_3N_3$ requires C, 58·8; H, 4·5; N, 17·1%). After storage for 3 months the material formerly melting at 190° had m. p. 222°.

(*b*) Methyl 3 : 4-dihydro-3-keto-4-methylquinoxaline-2-carboxylate (0·5 g.) (*J.*, 1951, 3379) was dissolved in excess of alcoholic ammonia (10%), and the precipitate was collected after 4 hours. 3-*Carbamyl*-1 : 2-*dihydro*-2-*keto*-1-*methylquinoxaline* (VI; R = NH_2) crystallised from water in pale yellow needles (0·25 g., 50%), m. p. 254—255° (Found: C, 59·2; H, 4·5; N, 20·2. $C_{10}H_9O_2N_3$ requires C, 59·1; H, 4·5; N, 20·7%). The amide (0·13 g.) was boiled with acetic anhydride (5 c.c.) for 30 minutes and the acetyl derivative (0·075 g., 48%), m. p. 190°, collected from the cold solution (Found: C, 58·4; H, 4·4; N, 17·0%). Crystallised from ethanol, it had m. p. 222° alone or mixed with the material prepared by method (*a*).

2-*Acetylcarbamyl*-3-*hydroxyquinoxaline* (VIII; R = NH·COMe).—(*a*) 3-Hydroxyquinoxaline-2-carboxyureide (VIII; R = NH·CO·NH_2) (3 g.) dissolved in *ca.* 5 hours when boiled with acetic anhydride (50 c.c.); boiling was then continued for 1 hour. Later, 2-*acetylcarbamyl*-3-*hydroxyquinoxaline* (0·8 g., 26%) was collected, and it crystallised from ethanol in yellow leaflets, m. p. 268° (decomp.) (Found: C, 57·5; H, 4·2; N, 18·1. $C_{11}H_9O_3N_3$ requires C, 57·1; H, 3·9; N, 18·2%). Evaporation of the filtrate and extraction of the residue with ethanol yielded further quantities of (VIII; R = NH·COMe), together with a colourless compound (0·4 g., 13%), rapid m. p. 266—267° (decomp.), probably an *acetyl* derivative of 3-hydroxyquinoxaline-2-carboxylic acid (Found: C, 56·9; H, 3·8; N, 12·1. $C_{11}H_8O_4N_2$ requires C, 56·9; H, 3·5; N, 12·1%).

(*b*) Ethyl 3-hydroxyquinoxaline-2-carboxylate (Gowenlock, Newbold, and Spring, *J.*, 1945, 622—625) (3 g.) in alcohol (20 c.c.) was mixed with alcoholic ammonia (10%; 50 c.c.). Amide formation (0·8 g., 31% after 4 hours; 98% after 72 hours) was much slower than with (VI; R = OMe) (above). 2-*Carbamyl*-3-*hydroxyquinoxaline*, which is sparingly soluble in hot water, crystallised in pale yellow needles, m. p. 308° (decomp.) (Found: C, 57·3; H, 3·7; N, 21·8. $C_9H_7O_2N_3$ requires C, 57·1; H, 3·7; N, 22·2%). Acetylation by boiling acetic anhydride for 30 minutes gave 2-acetylcarbamyl-3-hydroxyquinoxaline (68%), yellow leaflets, m. p. 266° (decomp.), alone and when mixed with the material obtained by method (*a*).

3-Hydroxyquinoxaline-2-carboxylic acid resists acetylation, the acid being recovered from short boiling with acetic anhydride. After 2½ hours' boiling, 2-hydroxyquinoxaline (25%), m. p. 270°, was obtained. Ethyl 3-hydroxyquinoxaline-2-carboxylate (2 g.) was boiled with acetic anhydride (20 c.c.) for 3 hours and the solution then evaporated to dryness. Repeated crystallisation from aqueous ethanol yielded original material (1·4 g., 70% recovery) and the more soluble *ethyl* 3-*acetoxyquinoxaline*(or 4-*acetylquinoxalone*)-2-*carboxylate* in colourless needles, m. p. 88—90°, clearing at *ca.* 130° (Found: C, 60·3; H, 4·3; N, 11·3. $C_{13}H_{12}O_4N_2$ requires C, 60·0; H, 4·6; N, 10·8%).

Quinoxaline-2-*carboxydimethylureides and Acetic Anhydride*.—3 : 4-Dihydro-3-keto-4-methylquinoxaline-2-carboxydimethylureide, which contains one active hydrogen atom (Found: active H, 0·46. Calc. for $C_{13}H_{14}O_3H_4$: active H, 0·36%), was recovered (75%) after 2½ hours' heating with acetic anhydride. In a similar experiment with the 4-phenyl analogue (Part I) the recovery was 80%.

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35. *The Interaction of Triphenylmethanol, Fluoren-9-ol, and Diphenylmethanol with Hydrazoic Acid in the Presence of Sulphuric Acid.*

By C. L. Arcus and R. J. Mesley.

By reaction with hydrazoic acid in the presence of sulphuric acid, triphenylmethanol yields azidotriphenylmethane, fluoren-9-ol yields phenanthridine and 9-azidofluorene, and diphenylmethanol yields aniline, benzaldehyde, and azidodiphenylmethane. 9-Azidofluorene has been prepared from 9-chlorofluorene; its acid-catalysed decomposition yields phenanthridine, and spontaneous decomposition (on storage or heating) yields 9-iminofluorene.

A mechanism, based on carbonium-ion formation, is proposed for the reaction of di- and tri-arylmethanols with hydrazoic and sulphuric acids.

In order to account for the observed products from the reaction of ketones, carboxylic acids, and olefins with hydrazoic acid in the presence of a strong acid, mechanisms have been proposed in which carbonium ions of the following forms are essential intermediates: for ketones the polarised molecule (I) (Briggs and Lyttleton, *J.*, 1943, 421) and the proton-adduct (II) (Sanford, Blair, Arroya, and Sherk, *J. Amer. Chem. Soc.*, **1945**, **67**, 1941; Newman and Gildenhorn, *ibid.*, 1948, **70**, 317; Smith, *ibid.*, p. 320), for carboxylic acids

$$\underset{\text{(I)}}{RR'\overset{+}{C}-\bar{O}} \qquad \underset{\text{(II)}}{RR'\overset{+}{C}-OH} \qquad \underset{\text{(III)}}{R\cdot\overset{+}{C}(OH)_2} \qquad \underset{\text{(IV)}}{R\cdot\overset{+}{C}=O} \qquad \underset{\text{(V)}}{Ar_2\overset{+}{C}-CH_3}$$

the proton-adduct (III) (Newman and Gildenhorn, *loc. cit.*; Schuerch and Huntress, *ibid.*, 1949, **71**, 2233; Arcus, Kenyon, and Levin, *J.*, 1951, 407) and its dehydro-form (IV) (Newman and Gildenhorn, *loc. cit.*), and for 1 : 1-diarylethylenes the proton-adduct (V) (McEwen, Gilliland, and Sparr, *J. Amer. Chem. Soc.*, 1950, **72**, 3212).

Numerous alkylations effected with di- and tri-arylmethanols have been recorded, and reaction probably proceeds *via* the carbonium ion:

$$RR'R''C^+ + HX \longrightarrow RR'R''CX + H^+$$

Further, di- and tri-arylmethanols form coloured solutions in sulphuric acid, a property attributed to the formation of carbonium ions (Balfe, Kenyon, and Searle, *J.*, 1950, 3309; Gold and Tye, *J.*, 1952, 2172, where earlier references are given), and cryoscopic measurements with such solutions yield van't Hoff *i* factors of approximately 4 (Newman and Deno, *J. Amer. Chem. Soc.*, 1951, **73**, 3644; Gold, Hawes, and Tye, *J.*, 1952, 2167, where earlier references are given), a value attributed (Newman, *J. Amer. Chem. Soc.*, 1941, **63**, 2431) to ionisation according to equation (1). In view of the evidence for the formation of carbonium ions from di- and tri-arylmethanols, it seemed probable that these alcohols would, in the presence of sulphuric acid, react with hydrazoic acid. The reaction with triphenylmethanol, fluoren-9-ol, and diphenylmethanol has been investigated; a preliminary note has appeared (*Chem. and Ind.*, 1951, 701).

The reaction with triphenylmethanol yielded azidotriphenylmethane; it is considered that the carbonium ion, formed as in (1), reacts with hydrazoic acid to give the proton-adduct of the azide (2), which releases a proton to yield the free azide (3).

$$RR'R''C\cdot OH + 2H_2SO_4 \longrightarrow RR'R''C^+ + H_3O^+ + 2HSO_4^- \quad . \quad . \quad . \quad . \quad (1)$$

$$RR'R''C^+ + HN_3 \longrightarrow RR'R''C\cdot NH\cdot\overset{+}{N}{:}N \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$RR'R''C\cdot NH\cdot\overset{+}{N}{:}N \xrightarrow{\text{Alternatively}} \begin{cases} \rightarrow H^+ + RR'R''C\cdot N_3 & . \quad . \quad . \quad . \quad . \quad (3) \\ \rightarrow N_2 + RR'C{:}\overset{+}{N}HR'' & . \quad . \quad . \quad . \quad . \quad (4) \end{cases}$$

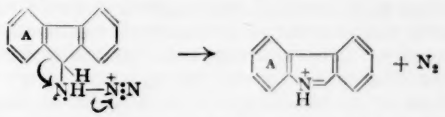
$$RR'C{:}\overset{+}{N}HR'' \longrightarrow H^+ + RR'C{:}NR'' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

$$RR'C{:}NR'' \xrightarrow{\text{Acid hydrol.}} RR'CO + R''\cdot NH_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Azidotriphenylmethane has been prepared by the action of nitrous acid on triphenylmethylhydrazine (Wieland, *Ber.*, 1909, **42**, 3026) and by the interaction of triphenylmethyl perchlorate with sodium azide (Lifschitz and Girbes, *Ber.*, 1928, **61**, 1488). Wieland found azidotriphenylmethane to be remarkably stable: it decomposed at about 180° when heated (Senior, *J. Amer. Chem. Soc.*, 1916, **38**, 2718, decomposed the azide at 225° and isolated benzophenone and aniline after hydrolysing the product) and, when the azide was added to sulphuric acid, a temperature of about 200° was required to effect appreciable decomposition. The azide is stable under the conditions of the present reaction, from which it was the main product.

The reaction with fluoren-9-ol yielded phenanthridine. In this instance the proton–azide adduct, formed as in (2), is considered to rearrange with loss of nitrogen to give the proton-adduct of an imine (4); loss of a proton yields the base (5), which is here a stable heterocycle, and reaction terminates at this stage. From one experiment, which gave a relatively low yield of phenanthridine, 9-azidofluorene was isolated, and this compound has also been prepared from 9-chlorofluorene and sodium azide. Reaction of 9-azidofluorene with sulphuric acid at 25° gave phenanthridine in good yield. On long storage or on heating, 9-azidofluorene decomposed to give 9-iminofluorene; this reaction, which is being further investigated, may proceed by a free-radical mechanism. It is concluded that the entity which undergoes rearrangement during the hydrazoic–sulphuric acid reaction is the proton-adduct of the azide and not the free azide.

The Schmidt reaction with (+)-α-phenylpropionic acid proceeds with a high retention of asymmetry and, probably, of configuration (Campbell and Kenyon, *J.*, 1946, 25), indicating the mechanism to be an intramolecular exchange of bonding at one face of the migrating carbon atom. From this result, together with the fact that the phenanthridine arises by a ring-expansion, the act of rearrangement, above, is considered to be intramolecular:



Electronic sharing between the migrating carbon atom of the ring A and the CH–NH fragment is continuous, and the four electrons initially present as the A–CH bond and the nitrogen lone-pair appear finally as the A–$\overset{+}{N}$H bond and the π-electrons of the $\overset{+}{N}$H=CH bond.

The reaction with diphenylmethanol yielded benzaldehyde and aniline. The products are considered to arise from hydrolysis (6) of the imine formed by reactions (1)—(5); this course for the reaction is in accord with the observation of Schmidt and Klavehn (D.R.-P. 583,565) that benzylideneaniline is produced by the reaction of thionyl chloride with a solution of diphenylmethanol in benzene containing hydrazoic acid. Azidodiphenylmethane has been isolated from the neutral, non-aldehydic fraction of the reaction products. Attempts to prepare the azide in larger quantity by interaction of diphenyl methyl chloride and sodium azide gave specimens which had suffered considerable loss of nitrogen. Reaction of the azide so prepared, and of the fraction containing the azide, with sulphuric acid at 25° yielded, in each case, aniline and benzaldehyde.

Equations (1)—(6) are proposed for the course of the reaction with di- and tri-arylmethanols; the stabilities of the compounds from the successive stages control the proportions in which these compounds appear in the final product from individual alcohols.

Improved preparations of the hydrazones of benzophenone and fluorenone are recorded.

Experimental

96% Sulphuric acid was used except where otherwise stated.

The Hydrazoic Acid–Sulphuric Acid Reaction.—(a) *With triphenylmethanol.* To a suspension of sodium azide (4·2 g.) in chloroform (13 ml.), cooled in ice, sulphuric acid (9 ml.) was slowly

added with stirring. The ice was replaced by a water-bath maintained at 25°, and a solution of triphenylmethanol (10 g.) in chloroform (40 ml.) added during 1 hour. Stirring was continued for ½ hour, ice (75 g.) was then added, and the mixture was kept overnight and filtered. The aqueous layer was extracted with ether. The combined ether and chloroform solutions were washed with water and dried (Na_2SO_4), and the solvents evaporated; addition of a little alcohol caused the separation of a solid (7·7 g.), which, recrystallised from alcohol, yielded azidotriphenylmethane, white needles (6·5 g.), m. p. 64° (Found: C, 80·0; H, 5·5; N, 14·5. Calc. for $C_{19}H_{15}N_3$: C, 80·0; H, 5·3; N, 14·7%). Wieland, and Lifschitz and Girbes, *locc. cit.*, record m. p. 64° and 65°. The filtrate from the above product yielded a small quantity of a 2 : 4-dinitrophenylhydrazone having m. p. 236—237° alone and when mixed with benzophenone 2 : 4-dinitrophenylhydrazone. The acid aqueous solution (above) was made alkaline with sodium hydroxide solution and extracted with ether; the extract yielded azidotriphenylmethane (0·2 g.).

(b) *With fluoren-9-ol.* To hydrazoic acid–sulphuric acid solution (from sodium azide, 2·7 g.; chloroform, 12 ml.; and sulphuric acid, 6·1 ml.), at 25°, a suspension of fluoren-9-ol (4·3 g.; m. p. 154—155°; Bachmann, *J. Amer. Chem. Soc.*, 1933, **55**, 772) in chloroform (23 ml.) was added in small portions during 20 minutes; stirring was continued for 1 hour, and crushed ice (100 g.) was then added. The mixture was warmed to 50°, stirred for 40 minutes, kept overnight, and filtered. The chloroform layer was shaken mechanically for 30 minutes with N-sulphuric acid (50 ml.) and washed with water. The aqueous part of the reaction mixture was shaken with chloroform (15 ml.). The two acidic aqueous solutions were combined and made alkaline with sodium hydroxide solution, warmed (to coagulate the precipitate), cooled and filtered. The phenanthridine so obtained crystallised from light petroleum (b. p. 60—80°) as rectangular plates, m. p. 106—107° [*mercurichloride*, buff needles, m. p. 195—198° (Found: Hg, 40·5; Cl, 21·3. $C_{13}H_9N,HCl,HgCl_2$ requires Hg, 40·4; Cl, 21·4%) (Pictet and Ankersmit, *Annalen*, 1891, **266**, 147, and Sielisch and Sandke, *Ber.*, 1933, **66**, 433, record m. p. 197° and 195—207°, but no analysis); picrate, m. p. 245° (Found: C, 56·3; H, 3·0; N, 13·6. Calc. for $C_{19}H_{12}O_6N_4$: C, 55·9; H, 3·0; N, 13·7%) (Pictet and Ankersmit, *loc. cit.*, give m. p. <220°)]. Evaporation of the combined chloroform solutions, above, yielded a non-basic oil. The yields from repetitions of hydrazoic acid–sulphuric acid reactions, despite efforts to maintain identical conditions, varied considerably. There was obtained: phenanthridine (i) 2·55 g., (ii) 1·94 g. (iii) 2·98 g.; non-basic material (i) 1·00 g., (ii) 1·64 g., (iii) 0·84 g. The non-basic material (ii) deposited crystals which on recrystallisation from aqueous alcohol yielded 9-*azidofluorene* (Found: C, 75·3; H, 4·4; N, 20·4. $C_{13}H_9N_3$ requires C, 75·3; H, 4·4; N, 20·3%), m. p. 41° and m. p. 43° when mixed with a specimen of m. p. 44—45° prepared as below.

Concentrated hydrochloric acid (200 ml.) containing fluoren-9-ol (22 g.) was boiled for 5 minutes. The solid product, recrystallised from light petroleum (b. p. 60—80°), yielded 9-chlorofluorene (20·5 g., 85%), needles, m. p. 90—91°. A solution of 9-chlorofluorene (20 g.) in methanol (60 ml.) was heated under reflux with sodium azide (10 g.) for 4 hours, then poured into water, and extracted with ether; the extract was washed with aqueous sodium hydroxide, and with water, dried (Na_2SO_4), and evaporated, giving a solid which yielded 9-azidofluorene (16 g., 77%), needles, m. p. 44—45° (from aqueous alcohol), readily soluble in chloroform, hot alcohol, or hot benzene, sparingly soluble in ether, light petroleum (b. p. 40—60°), or carbon disulphide. After 2 months 9-azidofluorene had become yellow and recrystallisation from ligroin (b. p. 100—120°) gave 9-iminofluorene, pale yellow needles, m. p. 124° (Found: C, 87·0; H, 5·1; N, 7·0. Calc. for $C_{13}H_9N$: C, 87·1; H, 5·1; N, 7·8%). Pinck and Hilbert (*J. Amer. Chem. Soc.*, 1934, **56**, 490) record m. p. 124°. The imine (1·0 g.) was heated under reflux for 30 minutes with sulphuric acid (30%; 40 ml.) and yielded fluorenone (0·87 g.), m. p. 83° alone or mixed with an authentic specimen. 9-Azidofluorene was gently heated above its m. p., vigorous decomposition occurring with formation of a solid which on recrystallisation from ligroin yielded the imine.

To 9-azidofluorenyl azide (4·9 g.) in chloroform (35 ml.), at 25°, sulphuric acid (6·1 ml.) was added dropwise, with stirring which was continued for a total of 30 minutes. Crushed ice (100 g.) was added and the mixture treated as described under (*b*), yielding phenanthridine (i) 3·5 g., (ii) 3·1 g., m. p. 106° alone or mixed with an authentic specimen (mercurichloride, m. p. 195—197°, mixed m. p. 195—198°). Evaporation of the final chloroform solution yielded an amorphous solid, (i) 1·0 g., (ii) 0·9 g., containing sulphur but not nitrogen, m. p. >300°.

(c) *With diphenylmethanol.* A solution of diphenylmethanol (10 g.) in chloroform (20 ml.) was allowed to react with a hydrazoic acid–sulphuric acid (from sodium azide, 5·5 g.; chloroform 17 ml.; and sulphuric acid, 9·2 ml.), with subsequent addition of ice (100 g.) and

warming, as described for fluoren-9-ol. Next morning the mixture was filtered from sulphur-containing material. The chloroform layer was shaken mechanically for 30 minutes with N-sulphuric acid (40 ml.). The acidic extract was combined with the aqueous part of the reaction mixture and extracted with ether. The aqueous layer was then made alkaline with sodium hydroxide solution and thrice extracted with ether, the extracts were washed with water, dried (Na_2SO_4), and evaporated, yielding aniline, b. p. 183°, n_D^{25} 1·5800 (benzoyl derivative, m. p. and mixed m. p. 161°). The chloroform and ether solutions were combined and evaporated, and the residue was shaken mechanically for 1 hour with a solution prepared as follows: sufficient water was added to sodium carbonate decahydrate (25 g.) to cover the crystals, and sulphur dioxide was passed until the solution was saturated. Chloroform (20 ml.) was added to the mixture, which was then filtered and separated. The solid bisulphite compound together with the aqueous solution was warmed with sulphuric acid (40%; 45 ml.) until the evolution of sulphur dioxide ceased; after cooling, the mixture was twice extracted with ether and the extract dried (Na_2SO_4). Evaporation of the ether yielded benzaldehyde, b. p. 178° (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 236°). In a control experiment 83% of the benzaldehyde originally present was isolated by this method. The chloroform extract of the bisulphite reaction mixture gave on evaporation a neutral liquid. There were obtained: aniline (i) 1·07 g., (ii) 2·05 g.; benzaldehyde (i) 0·48 g., (ii) 0·65 g.; neutral product (i) 8·4 g., (ii) 7·0 g. The neutral products were combined; distillation of a portion (2·5 g.) yielded *acidodiphenylmethane* (1·7 g.), b. p. 135°/4 mm., n_D^{22} 1·5883 (Found: C, 74·7; H, 5·3; N, 20·3. $C_{13}H_{11}N_3$ requires C, 74·6; H, 5·3; N, 20·1%). Another portion (5·0 g.) was dissolved in chloroform (12 ml.) and allowed to react with sulphuric acid (4 ml.) as described for 9-azidofluorene; crushed ice (100 g.) was added and the product kept overnight. It was separated as described above and yielded aniline (0·93 g.), benzaldehyde (0·90 g.), and neutral product (0·83 g.).

Two experiments were carried out as described under (*c*) except that 90% sulphuric acid (12·2 ml.) was used and diphenylmethanol (9·2 g.) in chloroform (20 ml.) was added during 1 hour and stirring continued for ½ hour; there were obtained: aniline (i) 1·6 g., (ii) 2·18 g.; benzaldehyde (i) 0·68 g., (ii) 1·15 g.; neutral product (i) 6·6 g., (ii) 4·3 g.

A solution of diphenylmethyl chloride (30 g.) in ethyl alcohol (99%; 45 ml.) (methanol and aqueous acetone were less satisfactory) was heated under reflux for 4 hours with sodium azide (15 g.). There was obtained impure azidodiphenylmethane (24 g.), b. p. 116—118°/1 mm., n_D^{21} 1·5702 (Found: C, 80·6; H, 6·9; N, 9·1%; Cl, 0), which by interaction with sulphuric acid, as described for the neutral product from (*c*), yielded aniline, benzaldehyde, and a neutral liquid product.

Benzophenone (19 g.), hydrazine hydrate (100%; 7 g.), and butyl alcohol (20 ml.) were heated under reflux for 3 hours. On cooling, a solid separated which on recrystallisation from alcohol (99%) yielded benzophenone hydrazone (11 g., 55%), rods, m. p. 99°. Fluorenone (8 g.), hydrazine hydrate (100%; 3·2 g.), and methanol (3 ml.) were heated under reflux on a water-bath for 5 minutes; the solid product, recrystallised from methanol, yielded fluorenone hydrazone (7·5 g., 89%), yellow needles, m. p. 148—149°. These preparations appear more satisfactory than, respectively, that of Curtius and Rauterberg (*J. pr. Chem.*, 1891, **44**, 194; *Org. Synth.*, 1944, **24**, 53) which employs ethyl alcohol in an autoclave for benzophenone hydrazone, and that of Wieland and Roseeu (*Annalen*, 1911, **381**, 231) which uses ethyl alcohol for fluorenone hydrazone and, as we have confirmed, yields fluorenone azine as a major product.

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36. *The Thermal Decomposition of Guanidine Perchlorate. Part I. Reaction Products and Mechanism.*

By Abraham Glasner and Abraham Makovky.

The behaviour of guanidine perchlorate at 300—450° has been studied, and from the analysis of the gaseous and (intermediate) solid products a tentative mechanism for the decomposition is proposed.

Although guanidine perchlorate may be expected to have more favourable properties as an explosive than, *e.g.*, ammonium perchlorate (Lothrop and Handrick, *Chem. Reviews*, 1949, **44**, 419), its thermal decomposition does not appear to have been studied. Pyrolysis of ammonium perchlorate has been investigated by Dode (*Bull. Soc. chim.*, 1938, **5**, 170) and that of the guanidine chromates by Chuk-Ching Ma (*J. Amer. Chem. Soc.*, 1951, **73**, 1333).

The following observations were made of the behaviour of guanidine perchlorate (m. p. 240°) at high temperatures and atmospheric pressure: (*a*) When it is heated at or below 300° for several hours it suffers only a very slight loss of weight. (*b*) Above 400° ignition occurs, but always after a definite period of initiation, and with the formation of a yellow solid residue. (*c*) In the range 300—400°, decomposition proceeds at a measurable rate and the reaction goes to completion.

The intermediate and the gaseous final products obtained at 340—390° are now described, and a mechanism for the thermal decomposition in this range is proposed.

Experimental

Guanidine perchlorate, prepared from the chloride and sodium perchlorate, and twice recrystallised from water, had m. p. 240° (Found: N, 25·9. Calc. for $CH_5N_3,HClO_4$: N, 26·3%).

The volume of the gases evolved was determined in Pyrex apparatus similar to that used by Glasner and Weidenfeld (*J. Amer. Chem. Soc.*, 1952, **74**, 2464). Temperatures were measured with a calibrated chromel–alumel couple and kept constant by manual regulation of a powerstat. Samples of 0·1 g. were used for each experiment, as larger quantities might be explosive, and the gases were analysed in the conventional manner.

The vacuum-apparatus has been described by Glasner and Simchen (*Bull. Soc. chim.*, 1951, **18**, 233). The initial pressure measured by the McLeod gauge was 6 μ; it rose by the end of the experiment (after 1 hour) to 9 mm. From the pressure and the known volume of the apparatus, the volume of the gases evolved was calculated.

For the determination of chlorides, the gases evolved and the apparatus were washed with distilled water. Aliquot parts of the solution thus obtained were titrated with 0·01N-sodium hydroxide and 0·1N-silver nitrate (Volhard).

Gaseous Products.—Analyses of the gases formed indicates that the thermal decomposition can be described by the equations:

$$2CH_5N_3,HClO_4 \longrightarrow 2HCl + 5H_2O + CO + CO_2 + 3N_2 \quad . . . . . (1)$$
$$2CH_5N_3,HClO_4 \longrightarrow 2HCl + 2NH_3 + O_2 + 2N_2 + 2CO_2 + 2H_2O \quad . . . . (2)$$

In addition, small quantities of chlorine, hydrogen, and (above 400°) nitrogen dioxide were formed. The amount of permanent gases collected was within 90—94% of that expected for both equations, *viz.*, 2·5 mols. The balance may be accounted for by a small residue of ammonium perchlorate.

From the amount of carbon monoxide or carbon dioxide, or from the ratio of free hydrogen chloride to ammonium chloride, the relative importance of the two reactions can be determined. The following data show that, generally, reaction (2) predominates, reaction (1) becoming more pronounced with increasing temperature.

Temp.	345°	370°	380°
HCl/NH_4Cl	24·4/75·6	38·6/61·4	39·5/60·5

The results for the relative weights of reactions (1) and (2), calculated from determinations of the carbon dioxide formed, accord well with those obtained from the chloride determinations;

e.g., the percentage of carbon dioxide in the gases obtained after complete decomposition at 370° was 32·3%, corresponding to a relative importance of 61·5% for reaction (2).

The total volume of gases obtained from the decomposition of the salt *in vacuo* at 350° was only 18% of that obtained at atmospheric pressure, and the greater part of the sample was converted into the above-mentioned yellow substance. This appears to be connected with the observation that, under these conditions, ammonium perchlorate is deposited on the cooler parts of the reaction vessel.

Solid Intermediates.—In the temperature range 320—390°, the molten salt gradually changed into a waxy solid before decomposing completely. When the reaction was stopped at this stage, the solid was found to consist partly of ammonium perchlorate; this dissolved in cold water, and the remainder of the solid was separated by boiling water into a soluble fraction (A) (Found: C, 18·8; H, 3·4; N, 39·8; Cl, 12·6; O, by diff., 25·4%) and an insoluble fraction (B) (Found: C, 19·8; H, 3·4; N, 41·3; Cl, 10·8; O, by diff., 24·7%) which, however, closely resembled A. The microanalyses are averages of a large number of runs. Neither of the products dissolved in any of the usual organic solvents or showed a definite m. p.; when heated, both turned into the " yellow solid " which decomposed above 500°. Their reactions with alkali, acid, and copper sulphate resembled those of melamine, ammeline, and melam (Bamberger, *Ber.*, 1883, **16**, 1074, 1703; Davis and Abrams, *Proc. Amer. Acad. Arts Sci.*, 1926, **61**, 437), so it can be assumed that the products represent mixtures of the perchlorates of these bases. The yellow product should therefore be mainly mellon.

It is in accord with these conclusions that similar products were obtained from guanidine chloride at about 350°, and that the products A and B as well as the yellow solid were oxidised completely to gaseous products when heated with potassium or ammonium perchlorate.

In the pyrolysis (at 355°) of guanidine perchlorate, a gradual increase in the nitrogen content of the insoluble residue is observed:

Time of reaction (min.)	20	33	75	150
N, %	33·55	35·53	44·7	46·65

Since ammonia is evolved with the gaseous products, this increase can best be explained by the assumption of an initial self-condensation of guanidine, followed by gradual conversion of the condensate into less basic substances of progressively smaller tendency to salt formation with perchloric acid.

Discussion

Mechanism of Decomposition.—The results support the following mechanism for the decomposition of the salt. (*a*) Ammonia is evolved, cyanamide and perchloric acid being formed; (*b*) cyanamide undergoes self-condensation, *e.g.*, to melamine:

$$CH_5N_3,HClO_4 \longrightarrow CN{\cdot}NH_2 + HClO_4 + NH_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

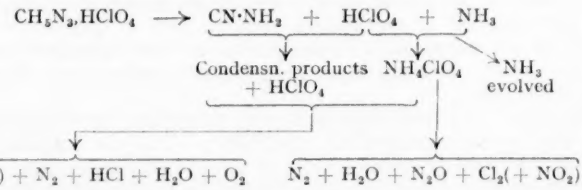
$$3CN{\cdot}NH_2 \longrightarrow C_3H_6N_6 \text{ (Melamine)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

(*c*) these condensation products are oxidised in stages, by perchloric acid or ammonium perchlorate, to the gaseous products found, amongst them hydrogen chloride, which may eventually combine with ammonia.

Under atmospheric pressure and at lower temperatures, ammonia will tend to evaporate preferentially and leave perchloric acid, which is available for the oxidation of the condensation products. At low temperatures, therefore, complete oxidation to carbon dioxide takes place, and a considerable amount of ammonium chloride is obtained (equation 2). As the temperature rises, or under reduced pressure, more perchloric acid enters the gas phase, thus reducing the oxygen available for oxidation of the solid, and increasing the proportion of carbon monoxide in the gaseous oxidation products (equation 1). Indeed, it has been shown that *in vacuo* almost complete evaporation of the ammonium perchlorate takes place, and the condensation to mellon proceeds undisturbed, as in the pyrolysis of guanidine chloride.

Above 390°, as observed by Dode (*loc. cit.*), the vaporised ammonium perchlorate explodes. The accompanying rise of temperature increases the rate of evaporation of the ammonium perchlorate and leads again to the formation of the yellow mellon. Under

these conditions the gaseous products are not only rich in oxygen, but also contain appreciable amounts of chlorine and nitrogen dioxide.



We are grateful to Prof. F. Bergmann, of the Hebrew University, for his interest and many helpful suggestions, and to Mrs. M. Goldstein for most of the microanalyses. These experiments were carried out under the auspices of the Scientific Department, Israeli Ministry of Defence, and are published with its permission.

THE HEBREW UNIVERSITY, JERUSALEM, ISRAEL. [*Received, October 4th*, 1952.]

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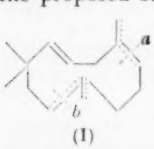
37. *The Chemistry of Humulene. Part III.**

By J. O. HARRIS.

Further investigation of the oxidation products of β-dihydrohumulene has led to the identification of succinic acid and ββ-dimethylpimelic acid. Formation of the latter is consistent with the formulation of humulene as a tetramethyl*cyclo*undecatriene. Less vigorous oxidation has resulted in the isolation also of a mono- or di-cyclic monoketo-carboxylic acid, $C_{15}H_{24}O_3$ (less probably $C_{15}H_{26}O_3$), and a dicyclic diketone, $C_{14}H_{22}O_2$. Attention is drawn to the resistance of α-tetrahydrohumulene to hydrogenolysis.

THAT the sesquiterpene humulene has a tetramethyl*cyclo*undecatriene structure (I) was suggested independently by Clemo and Harris (*Chem. and Ind.*, 1951, 799) and by Šorm, Streibl, Pliva, and Herout (*Chem. Listy*, 1951, **45**, 308; 1952, **46**, 30), the latter arguing from considerations of physical properties and the absence of large identifiable fragments on ozonolysis. In a further investigation of the products obtained from β-dihydrohumulene by potassium permanganate in acetone, followed by nitric acid (Clemo and Harris, Part II *), succinic and ββ-dimethylpimelic acid have been isolated. The former, because of its instability to potassium permanganate, presumably arises entirely from a secondary oxidation with nitric acid, and little structural significance can be attached to it. The formation of the latter acid, however, may be regarded as further substantive evidence for the proposed structure: it can arise by oxidation at points (*a*) and (*b*). Moreover the sequence $C{\cdot}C{\cdot}CMe_2{\cdot}C{\cdot}C{\cdot}C{\cdot}C$ can arise only from a seven-membered or larger ring. The possibility of a pimelic acid arising from the fission of a suitably substituted β-carboxy*cyclo*hexanone system cannot be entirely excluded—cf. the chemistry of irone (Ruzicka, Seidel, Schinz, and Pfeiffer, *Helv. Chim. Acta*, 1942, **25**, 188; 1947, **30**, 1807), although our experimental conditions, together with the inability to ketonize the C_{15} dicarboxylic acid obtained on the oxidation of tetrahydrohumulene (Clemo and Harris, *loc. cit.*), render this unlikely.

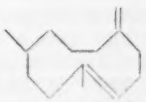


(I)

Oxidation of β-dihydrohumulene with potassium permanganate in acetone at 20—25° without subsequent treatment with nitric acid, gave *as*-dimethylsuccinic and ββ-dimethyladipic acid, together with a very small amount of a crystalline monoketo-carboxylic acid $C_{15}H_{24}O_3$ or $C_{15}H_{26}O_3$. Although the analytical data do not differentiate clearly between these two possibilities the former (presumably dicyclic) formula is preferred. It gives an ethyl ester 2 : 4-dinitrophenylhydrazone, and with alkaline hypoiodite a positive test for the acetyl group. The neutral fraction from this oxidation yielded a very small amount of a dicyclic diketone, $C_{14}H_{22}O_2$, which readily forms a bis-2 : 4-dinitrophenylhydrazone.

* Part II, *J.*, 1952, 665.

This substance is highly reminiscent of the tricyclic diketone $C_{14}H_{20}O_2$ from β-caryophyllene, the genesis of which has been elucidated by Barton (*J.*, 1951, 2988; 1952, 2210), and it is attractive to assume a similar mechanism, under the alkaline conditions employed, for the formation of our C_{14} diketone. This is most easily envisaged as arising from a structure such as (II *a* or *b*).

(II*a*)  (II*b*)

Tetrahydrohumulene monoxide has been prepared from tetrahydrohumulene by treatment with perbenzoic acid. In preliminary investigations this appears to be unusually resistant to hydrogenolysis (see p. 186). The resistance to fission of dihydro-β-caryophyllene monoxide has already been noted by Šorm, Dolyš, and Pliva (*Coll. Czech. Chem. Comm.*, 1950, **15**, 186), and this stability of oxides from large rings is of interest.

Experimental

Isolation of Succinic and ββ-Dimethylpimelic Acids.—Further investigation of fractions from the distillation of the methyl esters obtained by the oxidation of β-dihydrohumulene with potassium permanganate followed by nitric acid (Part II, *loc. cit.*) has given the following results. The fraction boiling at 100—110°/13 mm. (1·7 g.) was hydrolysed with methanolic potassium hydroxide. Chromatography of the crude free acidic material on silica gel, elution with ether, and purification by sublimation gave a colourless solid (30 mg.), m. p. 184° alone or mixed with authentic succinic acid (Found : C, 40·6; H, 5·2. Calc. for $C_4H_6O_4$: C, 40·7; H, 5·1%). The fraction boiling at 135—150°/13 mm. (4·0 g.) was similarly hydrolysed. The crude acid fraction distilled from a retort at 140—160° (bath-temp.)/0·01 mm. During 3—4 months at −5° the redistilled acids deposited a small amount of crystals, and decantation of the supernatant oil and repeated chromatography of a solution of the residual solid on silica gel, followed by elution with benzene–ether (3 : 2), gave a solid which recrystallized from concentrated hydrochloric acid in colourless prismatic needles (50 mg.), m. p. 100—101°, not depressed by authentic ββ-dimethylpimelic acid (Blanc, *Bull. Soc. chim.*, 1908, **4**, 286) (Found : C, 57·5; H, 8·6. Calc. for $C_9H_{16}O_4$: C, 57·4; H, 8·5%).

Oxidation of β-Dihydrohumulene with Potassium Permanganate.—Finely divided potassium permanganate was added with continuous stirring to β-dihydrohumulene (33 g.) in acetone (30 c.c.) during 2 days at 20—25° until a permanent pink colour remained. The filtered sludge was extracted with hot water, and the extract combined with the residue from the distillation of the acetone filtrate and extracted with ether (to remove neutral products). The aqueous layer was acidified and re-extracted with ether, and the crude acids obtained were esterified with an excess of ethereal diazomethane. The crude esters (22·0 g.) were submitted to repeated fractional distillation. The fraction (1·0 g.) of b. p. <53°/0·1 mm. was hydrolysed with methanolic potassium hydroxide; the crude acid obtained crystallized from concentrated hydrochloric acid in colourless prisms, m. p. alone or mixed with *as*-dimethylsuccinic acid 140—141° (Found : C, 49·5; H, 7·2. Calc. for $C_6H_{10}O_4$: C, 49·3; H, 6·9%). The fraction (1·7 g.) of b. p. 55—65°/0·1 mm. was similarly hydrolysed and the acids, after distillation in a retort at 120° (bath-temp.)/0·01 mm., were chromatographed on silica gel; elution with benzene–ether (1 : 1), sublimation at 100°/0·1 mm., and crystallization from concentrated hydrochloric acid gave colourless prisms, m. p. alone or mixed with authentic ββ-dimethyladipic acid 82—83° (Found : C, 54·9; H, 6·9. Calc. for $C_8H_{14}O_4$: C, 55·2; H, 8·1%).

The fraction (0·7 g.) of b. p. 92—97°/0·1 mm. was similarly hydrolysed and the crude acid was distilled in a retort at 110° (bath-temp.)/0·01 mm. Chromatography on silica gel and elution with benzene gave a fraction which solidified on trituration with light petroleum (b. p. 60—80°). Sublimation at 100°/0·1 mm. then gave white prisms (15 mg.), m. p. 160—161° (Found : C, 71·3; H, 9·8. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·5. $C_{15}H_{26}O_3$ requires C, 70·9; H, 10·3%). This *acid* gave a strong iodoform reaction with alkaline hypoiodite, and no colour with alcoholic ferric chloride. It did not decolorize permanganate in acetone, but in alcohol gave the ethyl ester 2 : 4-*dinitrophenylhydrazone* as yellow needles, m. p. 204° (from alcohol) (Found : C, 59·8; H, 7·0. $C_{23}H_{32}O_6N_4$ requires C, 60·0; H, 6·9. $C_{23}H_{34}O_6N_4$ requires C, 59·8; H, 7·9%).

The neutral fraction from the oxidation was distilled, giving fractions: (1) b. p. 57—70°/0·1 mm. (0·4 g.), (2) b. p. 71—81°/0·1 mm. (0·2 g.), and (3) b. p. 84—100°/0·1 mm. (0·5 g.). Fraction (1) yielded no solid derivative with Brady's reagent but evidence for the presence of the same ketonic material in fractions (2) and (3) was obtained with this reagent. These last fractions with semicarbazide in the usual manner gave a *semicarbazone* (50 mg.), needles (from aqueous alcohol), m. p. 137° (Found: C, 57·4; H, 8·6. $C_{16}H_{28}O_2N_6$ requires C, 57·2; H, 8·4%). Decomposition of the crude semicarbazone with aqueous oxalic acid and distillation of the product at 120° (bath-temp.)/0·1 mm. gave a fraction which solidified. Trituration of this with light petroleum (b. p. 60—80°) and sublimation at 55° (bath-temp.)/0·1 mm. gave a colourless *diketone*, m. p. 111° (Found: C, 75·6; H, 10·1. $C_{14}H_{22}O_2$ requires C, 75·7; H, 9·9%), insoluble in aqueous sodium hydroxide and giving no colour with alcoholic ferric chloride. In alcohol it gave a *bis*-2:4-*dinitrophenylhydrazone*, orange needles (from pyridine), m. p. 282—283° (Found: C, 53·6; H, 5·3. $C_2H_{30}O_8N_8$ requires C, 53·5; H, 5·2%).

Tetrahydrohumulene Monoxide.—Tetrahydrohumulene (3·0 g.) in chloroform (50 c.c.) was treated with a slight excess of perbenzoic acid and the mixture left overnight, then washed with aqueous sodium hydrogen carbonate, and water, dried and distilled. The *monoxide* was obtained as a colourless liquid (2·4 g.), b. p. 88°/0·1 mm., n_D^{17} 1·4770 (Found: C, 80·3; H, 12·7. $C_{15}H_{28}O$ requires C, 80·4; H, 12·6%).

It was unaffected by hydrogen in the presence of Adams's platinum oxide at room temperature and pressure. It was also recovered unchanged, as shown by refractive index, analysis and inactivity towards sodium and phosphorus pentachloride, after treatment with lithium aluminium hydride in ether at room temperature and on the boiling-water bath.

The author thanks Professor G. R. Clemo, F.R.S., for his continued interest and encouragement, and Messrs. White, Tompkin, and Courage, and Monsanto Ltd. for generous gifts of hop oil and clove oil terpene.

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38. *Triphenylethylenes and Related Compounds. Part IV.**

By WADIE TADROS, YOUSSEF AKHNOOKH, and GAMIL AZIZ.

New triphenylethylenes have been prepared and tested for œstrogenic activity.

THE presence of a *p*-bromine atom in the phenyl group marked *, like that of chlorine (Tadros, Farahat, and Robson, *J.*, 1949, 439), confers œstrogenic activity on substances of type $(Hal{\cdot}C_6H_4)_2C{:}CBrPh$* (Hal = Cl or Br). Substitution of a methyl group for either of these atoms causes even greater increase in the activity. On the other hand, the œstrogenic activity is suppressed on introduction of a *p*-cyano-group into the benzene nuclei. The significance of these findings cannot be explained in advance of a study of the metabolism of these compounds.

The introduction of a halogen atom into the ethylenic linkage of the triphenylethylenes reported herewith was accompanied by increase in potency (see Robson, Schönberg, and Fahim, *Nature*, 1938, **142**, 292; also Tadros and Aziz, *J.*, 1951, 2553).

The time required for the œstrogenic activity to fall to half was measured by the method described by Robson (*Quart. J. Exp. Physiol.*, 1938, **28**, 195) with Shorr's method for staining (*Science*, 1940, **91**, 579). The compounds were dissolved in sesame oil, and the œstrogenic activity was examined on injection subcutaneously into a group of 5 ovariectomised mice of average weight 22 grams (see Table 1 for results).

The triphenylethylenes were obtained by addition of *pp'*-disubstituted benzophenones to an ethereal solution of benzyl-, 4-bromobenzyl- or 4-methylbenzyl-magnesium bromide (excess of magnesium should be used for the last compound), followed by decomposition with aqueous ammonium chloride, the alcohols or triphenylethylenes being formed. Dehydration of the alcohols gave the triphenylethylenes and these were then chlorinated

* Part III, *J.*, 1952, 3823.

or brominated. 4-Cyano- and 4 : 4'-dicyano-benzophenone and 2-*p*-cyanophenyl-1 : 1-diphenylethylene were prepared from the corresponding bromo-compounds by a method slightly modified from that used by Bance, Barber, and Woolman (*J.*, **1943**, 1) for the

TABLE 1. $(p\text{-X}\cdot C_6H_4)_2C{:}CY\cdot C_6H_4Z\text{-}p$.

X	Y	Z	Dose (mg.)	Time (days)	X	Y	Z	Dose (mg.)	Time (days)
Cl	H	Br	5	∞	Br	Cl	Br	1	11
Br	H	Br	5	∞				5	15
$H_2CO\cdot CH_2Ph$	H	H	5	∞	Br	Br	Br	1	7
CN	H	H	5	∞	Cl	Br	Me	5	>90
Cl	H	Me	5	∞	OEt	Br	Br	0·1	8
OEt	H	Br	1	<125				0·5	>130
Cl	Cl	Br	5	12	H	H	CN	1	Slight activity

preparation of 4 : 4'-dicyanostilbene from 4 : 4'-dibromostilbene. 1 : 1-Di-*p*-ethoxyphenyl-2-*p*-nitrophenylethylene was obtained by Meerwein reaction from ββ-di-*p*-ethoxyphenylacrylic acid. ββ-Diphenylacrylic acids were prepared (*a*) by the method of Kharasch, Kane, and Brown (*J. Amer. Chem. Soc.*, 1942, **64**, 333) or (*b*) by hydrolysis of the ester obtained by Reformatsky reaction. Ethyl *p*-benzoylbenzimidate and *p*-amidinobenzophenone hydrochloride were also prepared but proved toxic.

EXPERIMENTAL

p-*Cyanobenzophenone*.—Freshly prepared, powdered cuprous cyanide (2·5 g.; previously dried at 110° for 36 hours) and *p*-bromobenzophenone (5 g.) were heated at 220° for 1 hour. Pyridine (2·5 c.c.) was then added and the mixture heated for further ½ hour at the same temperature and then decomposed with concentrated hydrochloric acid (50 c.c.). The solid material was filtered off through glass wool, washed with concentrated hydrochloric acid (20 c.c.) and then water, sublimed, and crystallised from ethyl alcohol from which it separated in pale yellow crystals (2·1 g.), m. p. 107—108° (Found : C, 80·9; H, 4·1; N, 6·6. Calc. for $C_{14}H_9ON$: C, 81·2; H, 4·3; N, 6·8%).

pp'-*Dicyanobenzophenone*.—Similarly prepared (*pp'*-dibromobenzophenone, 50 g.; cuprous cyanide, 39·2 g.; pyridine, 10 c.c.), this separated from acetic acid in colourless crystals (19·5 g.), m. p. 162° alone or mixed with an authentic sample (Ashley, Barber, Ewins, Newbery, and Self, *J.*, 1942, 103).

ββ-*Di*-p-*ethoxyphenylacrylic Acid*.—(*a*) (cf. Kharasch, Kane, and Brown, *loc. cit.*) *as*-Di-*p*-ethoxyphenylethylene (2 g.) (Tadros and Aziz, *loc. cit.*) and oxalyl chloride (3·75 g.) were mixed and left at room temperature until no more hydrogen chloride was evolved (0·5 hour). The mixture was then refluxed on the water-bath for 45 minutes and excess of oxalyl chloride was distilled off under reduced pressure. The syrupy residue was decomposed with cold aqueous sodium carbonate, and after 3 hours the whole was boiled for 10 minutes with charcoal and filtered. The filtrate was acidified with concentrated hydrochloric acid. The precipitate was dissolved in aqueous sodium carbonate and filtered from tar. The filtrate was acidified, and the precipitated *acid* crystallised from benzene as pale yellow needles (1·2 g.), m. p. 134° (Found : C, 72·3; H, 6·3. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·4%).

(*b*) Hydrolysis of ethyl ββ-di-*p*-ethoxyphenylacrylate (*A*) with alcoholic sodium ethoxide (1·25 mol.) gave the same acid, m. p. and mixed m. p. 133°.

The *ethyl* ester (*A*), m. p. 59° [from light petroleum (b. p. 30—50°)] (Found : C, 73·9; H, 6·8. $C_{21}H_{24}O_4$ requires C, 74·1; H, 7·0%), was prepared in *ca.* 45% yield by a Reformatsky reaction from *pp'*-diethoxybenzophenone (10 g.) in benzene–toluene.

ββ-*Di*-(p-n-*propoxyphenyl*)*acrylic acid*, prepared according to method (*a*) and crystallised from benzene, had m. p. 128—129° (0·52 g. from 2 g.) (Found : C, 74·5; H, 7·0. $C_{21}H_{24}O_4$ requires C, 74·1; H, 7·0%).

Grignard Reactions.—The alcohols were prepared by adding the appropriate *pp'*-disubstituted benzophenone (1 mol.) to the Grignard reagent from magnesium (2 atoms), 4-bromobenzyl chloride (1·8 mol.), and dry ether (1800 c.c.). In the case of the cyano-compounds 1·25 mol. of benzyl chloride and 1·25 atoms of magnesium were used. It was found necessary, however, to use excess of 4-methylbenzyl bromide (10 mol.) and double the equivalent of magnesium (20 atoms). The solutions were stirred after the addition of the ketones for 4 hours, then left

overnight, and the products were decomposed with aqueous ammonium chloride, extracted with ether or benzene–ether, and crystallised mainly from light petroleum (b. p. 40—60° or 60—80°) from which they separated in colourless or pale yellow crystals. Yields were about 40%.

During the preparation of 1-*p*-cyanophenyl-1 : 2-diphenylethanol, 1 : 2-diphenyl-1-*p*-phenylacetylphenylethanol was obtained. The latter was apparently formed by interaction of the cyano-alcohol first formed and excess of benzylmagnesium chloride.

The ethylenes were obtained either directly or by dehydration of the alcohol. The alcohol (1 g.) was heated in acetic acid (20 c.c.) containing acetyl chloride (20 c.c.) or concentrated sulphuric acid (0·5 c.c.), or was distilled in a vacuum in presence of one drop of 20% sulphuric acid. The solutions were poured into aqueous sodium carbonate, and the precipitated ethylenes were recrystallised from alcohol from which they separated in colourless crystals. For the *products* see Table 2.

TABLE 2.

Compound			M. p.	Found, %: C	H	Hal or N	Formula	Required, %: C	H	Hal or N
			Alcohols, *p*-X·C_6H_4·CH_2·$C(C_6H_4Y$-*p*$)(C_6H_4Z$-*p*$)$·OH.							
X	Y	Z								
H	CN	H	103—104°	84·3	5·6	4·6	$C_{21}H_{17}ON$	84·3	5·7	4·7
H	CO·CH_2Ph	H	144	85·4	6·2	—	$C_{28}H_{24}O_2$	85·7	6·1	—
H	CN	CN	194—195	80·9	5·2	8·4	$C_{22}H_{16}ON_2$	81·5	5·0	8·4
Br	Cl	Cl	109	57·7	3·5	35·5	$C_{20}H_{15}OCl_2Br$	56·9	3·6	35·8
Br	OEt	OEt	93	65·6	5·3	18·0	$C_{24}H_{25}O_3Br$	65·3	5·7	18·1
Me	Cl	Cl	120 *	70·6	5·3	19·4	$C_{21}H_{18}OCl_2$	70·6	5·0	19·9
			Ethylenes, *p*-X·C_6H_4·CH:$C(C_6H_4Y$-*p*$)$·C_6H_4Z-*p*.							
X	Y	Z								
H	CN	H	138—139	89·9	5·0	5·1	$C_{21}H_{15}N$	89·7	5·3	5·0
H	CN	CN	151	85·9	4·8	8·8	$C_{22}H_{14}N_2$	86·3	4·6	9·1
H	CO·CH_2Ph	H	110—111	90·2	5·7	—	$C_{28}H_{22}O$	89·9	5·9	—
Br	Cl	Cl	118	59·3	3·1	38·1	$C_{20}H_{13}Cl_2Br$	59·4	3·2	37·4
Br	Br	Br	101	48·7	2·8	48·4	$C_{20}H_{13}Br_3$	48·7	2·6	48·7
Br	OMe	OMe	107	67·1	4·8	19·5	$C_{22}H_{19}O_2Br$	66·9	4·8	20·2
Br	OEt	OEt	110	68·5	5·4	18·7	$C_{24}H_{23}O_2Br$	68·1	5·4	18·9
Me	Cl	Cl	94	73·8	4·7	21·6	$C_{21}H_{16}Cl_2$	74·3	4·7	20·9
			Halogenoethylenes, *p*-X·C_6H_4·CHal:$C(C_6H_4Y$-*p*$)_2$.							
X	Y	Hal								
Br	Cl	Cl	170—171	54·6	3·0	42·8	$C_{20}H_{12}Cl_3Br$	54·8	2·8	42·4
Br	Br	Cl	189	45·5	2·4	51·8	$C_{20}H_{12}ClBr_3$	45·5	2·3	52·1
Br	Cl	Br	174	50·0	2·6	48·4	$C_{20}H_{12}Cl_2Br_2$	49·7	2·5	47·8
Br	Br	Br	183 †	42·0	2·1	55·7	$C_{12}H_{12}Br_4$	41·9	2·1	55·9
Br	OMe	Br	114	55·7	4·0	34·1	$C_{22}H_{18}O_2Br_2$	55·7	3·8	33·7
Br	OEt	Br	99	57·3	4·4	32·0	$C_{24}H_{22}O_2Br_2$	57·3	4·4	31·9
Me	Cl	Br	158	60·5	3·6	35·5	$C_{21}H_{15}Cl_2Br$	60·3	3·6	36·1

* Contaminating 4 : 4′-dimethyldibenzyl should be removed, before recrystallisation, by steam-distillation. † This compound, m. p. 184—185°, was obtained (Buckles, Hansman, and Wheeler, *J. Amer. Chem. Soc.*, **1950**, **72**, 2494) by bromination of solid triphenylethylene and bromoethylene with bromine vapour.

1 : 1-*Di*-p-*ethoxyphenyl*-2-p-*nitrophenylethylene*.—To a solution of ββ-di-*p*-ethoxyphenylacrylic acid (4 g.) in acetone (100 c.c.) at 5°, a solution of diazotised *p*-nitroaniline (from 1·8 g. of *p*-nitroaniline), solid sodium acetate (3·5 g.), and aqueous cupric chloride (1 g. in 10 c.c. of water) were added. The temperature was allowed to rise slowly. Reaction started at 25° with evolution of gas which subsided after 20 minutes. The mixture was heated at 35° for 1 hour, then steam-distilled, and the semi-solid residue was taken up with benzene, washed with alkali, and then water, and evaporated. The residue was fractionally crystallised from alcohol from which *as*-di-*p*-ethoxyphenylethylene (1·55 g.), m. p. and mixed m. p. 142°, separated first. The mother-liquor was concentrated and the *triphenylethylene* separated thereafter in colourless crystals (0·72 g.), m. p. 88° (Found: C, 73·8; H, 6·1; N, 4·0. $C_{24}H_{23}O_4N$ requires C, 74·0; H, 5·9; N, 3·6%).

2-p-*Cyanophenyl*-1 : 1-*diphenylethylene*, prepared from 2-*p*-bromophenyl-1 : 1-diphenylethylene (Tadros, Farahat, and Robson, *loc. cit.*) by cuprous cyanide, etc., separated from alcohol in pale yellow crystals, m. p. 107—109° (Found: N, 4·3. $C_{21}H_{15}N$ requires N, 5·0%).

Ethyl p-*Benzoylbenzimidate*.—Powdered *p*-cyanobenzophenone (5 g.) was suspended in dry benzene (200 c.c.) and absolute alcohol (1 g.); the solution was saturated with hydrogen

chloride at −5° and left for 10 days at room temperature. Light petroleum (b. p. 60—70° 250 c.c.) was added, and the crystalline product which separated out on cooling in ice was filtered off (yield, 2·3 g.). This proved on analysis to be a mixture of the base and its hydrochloride and was treated with aqueous sodium carbonate; the *ester*, washed with distilled water and crystallised from benzene, had m. p. 164° (Found: C, 75·4; H, 5·9; N, 5·6. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 6·0; N, 5·5%).

p-*Amidinobenzophenone Hydrochloride*.—A solution of ammonia (1 g.) in absolute alcohol (12 c.c.) was added to a solution of the crude foregoing hydrochloride (1·5 g.) in the same solvent (50 c.c.) and the mixture was kept at room temperature with occasional shaking for 3 hours; the solution was filtered and freed from alcohol, and the residue fractionally crystallised from benzene whereby unchanged ester (0·35 g.), m. p. and mixed m. p. with an authentic sample 163°, separated. The material recovered from the benzene mother-liquor was dissolved in methyl alcohol (2 c.c.), the solution was filtered, and dry ether (10 c.c.) was added. The crude *amidine hydrochloride* (0·72 g.) was further crystallised from dry benzene from which it separated in colourless crystals, m. p. 196° (1 mol. of methyl alcohol of crystallisation was not removed in vacuum-desiccator over $CaCl_2$) (Found: C, 61·9; H, 5·4; N, 9·7; Cl, 12·5. $C_{14}H_{13}ON_2Cl,CH_3{\cdot}OH$ requires C, 61·5; H, 5·7; N, 9·6; Cl, 12·1%).

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39. *Quaternary Ammonium Salts. Part III.**

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On degradation of the quaternary ammonium salts of two esters, the ester groups were hydrolysed before decomposition affected the ammonium group. Quaternary ammonium derivatives have been prepared from some *as*-diphenylethylenes. Condensation of dimethylaniline with acetyl chloride in presence of fused zinc chloride gave rise to ααα-tris-*p*-dimethylaminophenylethane.

DEGRADATION of *p*-carbomethoxyphenyltrimethylammonium iodide (Tadros and Kamel, unpublished work) and 2-carbethoxy-1 : 1-diphenylethylene-*pp'*-bistrimethylammonium iodide, $CO_2Et{\cdot}CH{:}C(C_6H_4{\cdot}NMe_3I)_2$, with boiling methanolic sodium methoxide gave *p*-dimethylaminobenzoic and bis-*p*-dimethylaminophenylacrylic acid respectively. In view of the electron-attracting properties of the carbomethoxy- and carbethoxy-groups (see, *e.g.*, Zaki, *J.*, 1928, 983) it was expected that the degradation of the above two ester quaternary ammonium iodides would have resulted in the production of some methyl *p*-anisoate and ethyl di-*p*-methoxyphenylacrylate (or the derived sodium salts) as in known cases (Zaki and Tadros, *J.*, 1941, 350; Zaki and Fahim, *J.*, 1942, 271; Tadros and Latif, *J.*, 1949, 3337). It was found that with both the ester quaternary iodides in methanolic sodium methoxide at room temperature the ester group was hydrolysed before degradation affected the ammonium group. This result probably explains the failure to obtain the expected methoxy-esters, since (*a*) the carboxyl ion has little or no attraction for electrons and (*b*) *p*-carboxyphenyltrimethylammonium chloride and sodium ethoxide (Zaki and Tadros, *J.*, 1941, 562) did not give *p*-ethoxybenzoic acid.

The preparative work recorded in the Experimental followed substantially known procedures.

EXPERIMENTAL

M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.

Ethyl ββ-*Bis*-p-*dimethylaminophenylacrylate*.—This was prepared by Reformatsky's reaction (zinc needles, 32·7 g.; dry benzene, 300 c.c.; Michler's ketone, 26·6 g.; ethyl bromoacetate, 33·5 g.). When the reaction subsided, the mixture was refluxed for 3 hours, and the cooled benzene solution decanted from black material. The benzene solution was shaken twice with hydrochloric acid (1 : 1). To the acid extract sodium hydroxide solution was added until the solution became weakly acidic and the precipitated Michler's ketone was filtered off. The

* Part II, *J.*, 1951, 1890.

filtrate was made alkaline and the semi-solid material thus precipitated was taken up with ether. The ethereal extract was extracted with hydrochloric acid and the acid solution treated with sodium hydroxide as before, this being repeated until the *ester* was obtained free from unchanged ketone. It separated from light petroleum (b. p. 40—60°) in yellow crystals, m. p. 98—100° (Found: C, 74·4; H, 7·7; N, 8·3. $C_{21}H_{26}O_2N_2$ requires C, 74·5; H, 7·7; N, 8·3%). The black residue was dissolved in concentrated hydrochloric acid, the mixture filtered, and the filtrate made alkaline with sodium hydroxide solution. The precipitate thus obtained was filtered off and the process repeated twice. The final material was redissolved in hydrochloric acid and the solution treated with sodium hydroxide drop by drop and the precipitate (5 g.) which separated in the slightly acid medium was collected. This separated after several crystallisations from benzene–light petroleum (b. p. 60—80°) in almost colourless crystals, m. p. 211°. It proved to be tetrakis-*p*-dimethylaminophenylpinacol, showing no depression in m. p. on admixture with an authentic sample (Gomberg and Bachmann, *J. Amer. Chem. Soc.*, 1927, **49**, 236) (Found: C, 76·2; H, 7·6; N, 10·4. Calc. for $C_{34}H_{42}O_2N_4$: C, 75·8; H, 7·7; N, 10·4%). The slightly acid filtrate was made alkaline and more acrylic ester was obtained (total yield, 10%).

ββ-*Bis*-p-*dimethylaminophenylacrylic Acid*.—(*a*) The ester (3 g.) and methyl-alcoholic sodium methoxide (from 1 g. of sodium in 20 c.c. of methyl alcohol) was refluxed for 2 hours. The alcohol was distilled off and the residue taken up with water and filtered off. Dilute acetic acid was added drop by drop to the filtrate whereupon the *acid* separated. It crystallised from benzene in greenish crystals, m. p. 172—173° (Found: C, 73·7; H, 7·1; N, 9·2. $C_{19}H_{22}O_2N_2$ requires C, 73·6; H, 7·1; N, 9·0%).

(*b*) *as*-Bis-*p*-dimethylaminophenylethylene (2·5 g.) and oxalyl chloride (4·5 g.) were refluxed for 2 hours. Excess of oxalyl chloride was removed *in vacuo* and the semi-solid dark residue was treated with excess of 10% sodium carbonate solution. The mixture was boiled and then filtered. The filtrate was neutralised with dilute acetic acid whereupon the acid separated (yield, 2%).

ααα-*Tris*-p-*dimethylaminophenylethane*.—Acetyl chloride (10 g.), dimethylaniline (50 g.), and fused zinc chloride (5 g.) were heated on the water-bath with stirring for 4 hours, decomposed with water, made alkaline, and steam-distilled and the semi-solid black *triamine* was crystallised several times from benzene–ether from which it separated in almost colourless crystals, m. p. 205—206° (30%) (Found: C, 80·4; H, 8·7; N, 10·3. $C_{26}H_{33}N_3$ requires C, 80·6; H, 8·5; N, 10·8%).

Tetrakis-p-*dimethylaminophenylethylene*.—To the Grignard reagent prepared from magnesium (5·8 g.), *iso*propyl iodide (42·5 g.), and ether (200 c.c.), Michler's ketone (13·3 g.) was added (cf. Lemoult, *Compt. rend.*, 1912, **154**, 1622). The solution was stirred for 4 hours on the water-bath, decomposed with aqueous ammonium chloride, and extracted with ether. A part of the residue left after removal of the ether dissolved in alcohol and proved to be 1 : 1-bis-*p*-dimethylaminophenyl*iso*butene. The alcohol-insoluble *tetra-amine* (3 g.) separated from benzene–light petroleum (b. p. 60—80°) in greenish crystals, m. p. 296° (Found: C, 80·4; H, 7·9; N, 11·3. Calc. for $C_{34}H_{40}N_4$: C, 80·9; H, 7·9; N, 11·1%).

as-*Bis*-p-*dimethylaminophenylethylene*.—To the Grignard reagent prepared from magnesium (1·2 g.), *p*-bromodimethylaniline (9·7 g.), and ether (100 c.c.), redistilled ethyl acetate (5 g.) was added. After 2 hours' stirring, the solution was left overnight and then decomposed with aqueous ammonium chloride. Ether was distilled off and the residue gave after several crystallisations from alcohol 50 mg. of the pure ethylene, m. p. 118° alone or mixed with an authentic sample.

Oxidation of 1 : 1-*Diphenylethylene*-pp'-*bistrimethylammonium Chloride*.—A solution of the salt (1·0 g.) in concentrated nitric acid (20 c.c.; *d* 1·42) was refluxed on a sand-bath for 4 hours, then evaporated to dryness on the water-bath, and the residue was treated twice with 10 c.c. of concentrated hydrochloric acid and evaporated almost to dryness after each treatment. The dipicrate prepared from the residue proved to be benzophenone-*pp'*-bis(trimethylammonium picrate) (Tadros and Latif, *loc. cit.*), m. p. and mixed m. p. 206—208°.

Quaternary Ammonium Salts of as-*Diphenylethylenes*.—*The dipicrates*. The base (1 mol.) and methyl sulphate (4 mol.) were heated on the water-bath, the vigorous exothermic reaction being controlled by cooling. The mixture was then heated on the water-bath for 3 hours. The methosulphates were not isolated and were converted into the dipicrates from which the dichlorides, dibromides, di-iodides (also obtained by refluxing for several hours the base with excess of methyl iodide in methyl alcohol and then distilling off the solvent and excess of methyl iodide), and diperchlorates were obtained as previously reported (cf. Zaki and Tadros, *loc. cit.*).

Products are reported in the Table. They are soluble in water and alcohol, but insoluble in ether, benzene, or acetone. The dichlorides, dibromides, and di-iodides are hygroscopic and retain solvent of crystallisation (particularly alcohol) which could only be removed after heating at 100° for considerable time *in vacuo* over P_2O_5 or $CaCl_2$.

p-Carbomethoxyphenyltrimethylammonium iodide, m. p. 170° (cf. Willstätter and Kahn, *Ber.*, 1904, **37**, 401), was prepared from the ester (5 g.) and methyl iodide (50 g.) on the water-bath for 10 hours. The derived *picrate*, m. p. 180°, crystallised from alcohol in yellow crystals (Found: C, 48·3; H, 4·5; N, 13·9. $C_{17}H_{18}O_9N_4$ requires C, 48·3; H, 4·3; N, 13·3%). *p*-Carboxyphenyltrimethylammonium chloride, m. p. 240° (decomp.), which was obtained from *p*-carboxyphenyltrimethylammonium picrate, m. p. 206—207° (Zaki and Tadros, *loc. cit.*), was also obtained on treatment of the ester picrate with concentrated hydrochloric acid.

Decomposition of the quaternary ammonium salts. A mixture of the halide (5 g.) and methyl-alcoholic sodium methoxide (20 c.c.; 2·5 atoms of sodium per 1 mol. of the salt) was refluxed for 4 hours on the water-bath. Methyl alcohol was evaporated off and the residue treated with hydrochloric acid. A clear solution was obtained which was neutralised with sodium hydroxide drop by drop until a precipitate was formed. This separated from alcohol and was proved by m. p. and mixed m. p. to be the corresponding tertiary base.

The same result was obtained on decomposition with alcoholic sodium ethoxide, phenoxide, or benzyloxide.

		Found, %:					Required, %:			
Salt	M. p.	C	H	N	Hal	Formula	C	H	N	Hal
1 : 1-*Diphenylethylene*-pp′-*bistrimethylammonium*										
picrate	216—218°	51·0	4·3	14·3	—	$C_{32}H_{32}O_{14}N_8$	51·1	4·3	14·9	—
chloride	122—135 *†	65·1	7·7	7·8	18·2	$C_{20}H_{28}N_2Cl_2$	65·4	7·6	7·6	19·4
bromide	218 *	52·3	6·2	6·0	34·9	$C_{20}H_{28}N_2Br_2$	52·6	6·1	6·1	35·1
iodide	198 *	43·4	5·5	4·9	45·9	$C_{20}H_{28}N_2I_2$	43·6	5·1	5·1	46·2
perchlorate ...	242 *	48·1	5·7	6·1	14·8	$C_{20}H_{28}N_2Cl_2O_8$	48·5	5·7	5·7	14·4
1 : 1-*Diphenyl*-2-*methylethylene*-pp′-*bistrimethylammonium*										
picrate	181—184	51·6	4·5	14·2	—	$C_{33}H_{34}O_{14}N_8$	51·7	4·4	14·6	—
chloride	164 *	66·6	8·1	6·8	18·3	$C_{21}H_{30}N_2Cl_2$	66·1	7·9	7·4	18·6
bromide	180 *	53·1	6·1	6·2	34·5	$C_{21}H_{30}N_2Br_2$	53·6	6·4	5·9	34·1
iodide	160 *	45·1	5·1	5·5	44·7	$C_{21}H_{30}N_2I_2$	44·7	5·3	5·0	45·0
perchlorate ...	250—252 *	50·0	6·0	5·3	14·7	$C_{21}H_{30}N_2Cl_2O_8$	49·5	5·9	5·5	13·9
1 : 1-*Diphenyl*-2-*ethylethylene*-pp′-*bistrimethylammonium*										
picrate	148—150	51·9	4·3	14·5	—	$C_{34}H_{36}O_{14}N_8$	52·3	4·6	14·4	—
chloride	169 *	66·6	8·0	6·8	17·9	$C_{22}H_{32}N_2Cl_2$	66·8	8·1	7·1	18·0
bromide	231—232 *	54·3	6·1	6·2	32·8	$C_{22}H_{32}N_2Br_2$	54·5	6·6	5·9	33·0
iodide	224 *	45·4	5·5	4·3	43·5	$C_{22}H_{32}N_2I_2$	45·6	5·5	4·9	43·9
perchlorate ...	248—250 *	50·1	6·1	5·2	13·8	$C_{22}H_{32}O_8N_2Cl_2$	50·5	6·1	5·4	13·6
1 : 1-*Diphenyl*-2 : 2-*dimethylethylene*-pp′-*bistrimethylammonium*										
picrate	205—206	52·4	4·3	14·3	—	$C_{34}H_{36}O_{14}N_8$	52·3	4·6	14·4	—
chloride	143 *	66·5	8·3	6·8	17·8	$C_{22}H_{32}N_2Cl_2$	66·8	8·1	7·1	18·0
bromide	200—201 *	54·1	6·8	6·2	33·5	$C_{22}H_{32}N_2Br_2$	54·5	6·6	5·8	33·0
iodide	218 *	45·9	5·6	4·5	43·6	$C_{22}H_{32}N_2I_2$	45·6	5·5	4·9	43·9
perchlorate ...	280 *	50·1	6·1	5·3	13·9	$C_{22}H_{32}O_8N_2Cl_2$	50·5	6·1	5·4	13·6
2-*Carbethoxy*-1 : 1-*diphenylethylene*-pp′-*bistrimethylammonium*										
iodide	174	44·4	5·1	4·4	40·6	$C_{23}H_{32}O_2N_2I_2$	44·5	5·1	4·5	40·8
picrate	85—90	—	—	13·7	—	$C_{35}H_{36}O_{16}N_8$	—	—	13·6	—
2-*Carboxy*-1 : 1-*diphenylethylene*-pp′-*bistrimethylammonium*										
picrate	122—124	—	—	13·8	—	$C_{33}H_{32}O_{16}N_8$	—	—	14·1	—

* With decomp. Most of the salts become green some degrees below the m. p. † Extremely hygroscopic and retains HCl, the latter being removed *in vacuo* at 100° over P_2O_5.

Hydrolyses of the ester group before decomposition of the quaternary ammonium group. (*a*) Methyl-alcoholic sodium methoxide (from 0·1 g. of sodium in 20 c.c. of methyl alcohol) containing *p*-carbomethoxyphenyltrimethylammonium iodide (1 g.) was left at room temperature (25—30°). A sample was daily left to evaporate at room temperature and the residue converted into the picrate. The picrate obtained after 4 days had m. p. 206—208° alone or mixed with *p*-carboxyphenyltrimethylammonium picrate (Zaki and Tadros, *loc. cit.*). (*b*) 2-Carbethoxy-1 : 1-diphenylethylene-*pp*′-bistrimethylammonium iodide, when treated as above, gave the carboxymethylene salt, m. p. 122—124°.

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40. *Experiments on the Synthesis of Aza-steroids. Part I.*

By G. R. Clemo and L. K. Mishra.

Syntheses of 15 : 16-dihydro-11-aza*cyclo*penta[*a*]phenanthrene* and certain related substances have been achieved.

Certain alkaloids such as solanine, veratrine, and conessine which show interesting physiological properties have been shown to be steroid derivatives (Soltys and Wallenfels, *Ber.*, 1936, **69**, 811; Clemo, Morgan, and Raper, *J.*, 1936, 1299; Jacobs and Sato, *J. Biol. Chem.*, 1948, **175**, 57; Haworth *et al.*, *J.*, 1949, 831; 1951, 1371). Besides these natural products, many basic steroids have been synthesised for biological study (Antarci and Petrow, *J.*, 1951, 901; Marjori, Hutton, and Webb, *J.*, 1951, 2767; Dodgson and Haworth, *J.*, 1952, 67). All these, however, contain the basic group outside the *cyclo*penta[*a*]-phenanthrene ring; the only known steroids which contain the nitrogen in the ring are 4-aza-derivatives (Bolt, *Rec. Trav. chim.*, 1938, **57**, 905; U.S.P. 2,227,876) which have been synthesised from natural steroids. Cook and Thomson prepared 6-azachrysene, 1-azapyrene, and 3 : 4-benz-5-azaphenanthrene (*J.*, 1945, 395) for the study of their carcinogenic properties. Buu-Hoï also obtained interesting results for some polycyclic aza-compounds (*J.*, 1952, 2225). It was considered therefore that aza-steroids (compounds containing a nitrogen atom in different positions of the steroid skeleton) might possess interesting physiological properties and also assist in the elucidation of the structure of such phenanthridine alkaloids as tazzetine, chelidonine, delphinine, and lycorine.

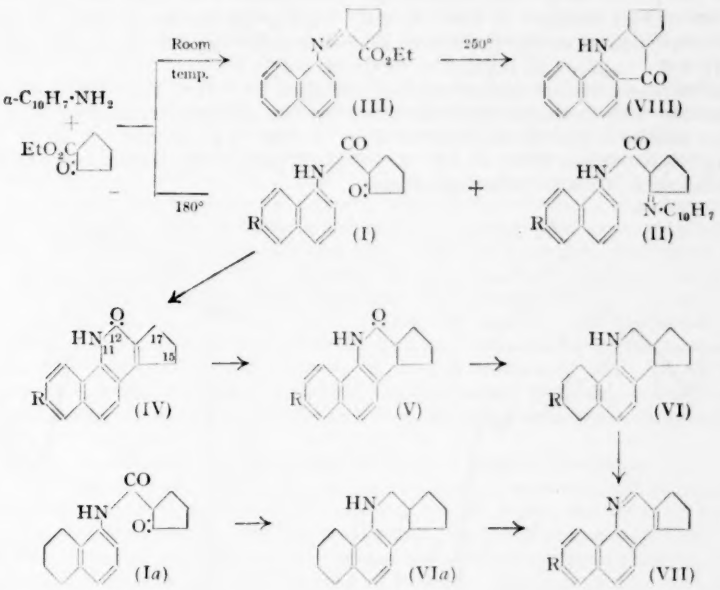
Our first syntheses started from α-naphthylamine which when heated with ethyl 2-keto*cyclo*pentanecarboxylate gave two products, (I and II; R = H). The naphthalide (I; R = H) gave a deep blue colour with ferric chloride and a crystalline 2 : 4-dinitrophenylhydrazone. Ring closure of (I; R = H) by concentrated sulphuric acid yielded a high-melting solid (IV; R = H) which is insoluble in both dilute acid and alkali and is sparingly soluble in organic solvents. An alcoholic solution of (IV; R = H) gives a light brown colour with ferric chloride which is characteristic of the 2-pyridone and 2-quinolone systems, and, like the quinolone, (IV) can react in the 12-hydroxy-form. Catalytic reduction of this compound failed because of its sparing solubility, but sodium amalgam in boiling ethanol yielded a dihydro-product (V; R = H) which was reduced by sodium in boiling alcohol to a secondary base (VI; R = H). When (IV; R = H) was heated with phosphorus oxychloride, the 12-chloro-compound was obtained in moderate yield, but attempts to reduce this chloro-compound to a secondary base by sodium and alcohol gave 12-ethoxy-15 : 16-dihydro-11-aza*cyclo*penta[*a*]phenanthrene. Catalytic reduction of 12-chloro-15 : 16-dihydro-11-aza*cyclo*penta[*a*]phenanthrene with palladium–charcoal in acetic acid (*Org. Synth.*, **26**, 45) as well as with Adams's platinum oxide failed to give 15 : 16-dihydro-11-aza*cyclo*pent[*a*]phenanthrene. Mikailov's method (*J. Gen. Chem., U.S.S.R.*, 1936, **6**, 511) of reducing 2-chlorolepidine to lepidine also proved unsuccessful in this case, but a small quantity of (VI; R = H) was obtained when this chloro-compound was reduced with tin and alcoholic hydrochloric acid at 100°. Dehydrogenation of (VI; R = H) with selenium gave a crystalline base (VII; R = H) the melting point (130°) of which was very near to that of *cyclo*penta[*a*]phenanthrene (m. p. 134°) and which readily gave a methiodide. This, however, did not give the expected *pseudo*-base with the grouping $\mathrm{MeN}\text{–}\mathrm{CH}\cdot\mathrm{OH}$ on treatment with alkali, (VII; R = H) being recovered.

Attempts to introduce a keto-group into the 15- or the 17-position of (VII; R = H) by chromic acid or selenium dioxide failed.

At room temperature α-naphthylamine and ethyl 2-keto*cyclo*pentanecarboxylate gave a crystalline Schiff's base (III; R = H) which neither gave a colour with ferric chloride nor formed a 2 : 4-dinitrophenylhydrazone. Ring closure of this compound at 250° (Conrad and Limpach, *Ber.*, 1887, **20**, 944; 1931, **64**, 969) gave a high-melting, sparingly soluble substance (VIII; R = H) which resembled its isomer (IV; R = H).

* Ring Index names [steroid numbering except for (VIII)] are used in this paper.

When α-naphthylamine was replaced as starting material by 5 : 6 : 7 : 8-tetrahydro-1-naphthylamine, the reactions gave a series of reduced compounds up to the secondary base (VI*a*). This on selenium dehydrogenation gave a product identical with (VII; R = H). Although the secondary bases (VI) and (VI*a*) have similar ultra-violet spectra and analyses and give the same product on dehydrogenation, they had different melting points and the mixed melting point was depressed by 10°. We suggest that they are



cis- and *trans*-forms of 1 : 2 : 3 : 4 : 11 : 12 : 13 : 14 : 15 : 16-decahydro-11-aza*cyclo*penta[*a*]-phenanthrene. From the work of Skita (*Annalen*, 1923, **431**, 1) the higher-melting base (VI) which was also obtained by the reduction of the chloro-compound in acid solution may be considered the *cis*-form.

The same reactions were also carried out with 6-methoxy-1-naphthylamine and compounds up to the dihydro-product (V; R = OMe) obtained, but this could not be reduced to (VI; R = OMe).

An attempt was made to prepare (VI; R = H) with a 13-methyl group, but ethyl 2-keto-1-methyl*cyclo*pentanecarboxylate did not condense with α-naphthylamine. We also tried unsuccessfully to condense methylacrylonitrile and methyl methylacrylate with α-naphthylamine, although acrylonitrile gave good yields of condensation product. Bruson (*Org. Reactions*, Vol. V, p. 108) has also observed that methylacrylonitrile is much less reactive than acrylonitrile in the cyanoethylation of aromatic amines. Thus the introduction of the methyl group by direct synthesis does not seem possible. Other methods of introducing the 13-methyl group are being investigated.

The ultra-violet absorption spectra of 15 : 16-dihydro-11-aza*cyclo*penta[*a*]phenanthrene (VII) is similar to that of 15 : 16-dihydro*cyclo*penta[*a*]phenanthrene (Mayneord and Roe, *Proc. Roy. Soc.*, 1935, *A*, **152**, 299; Harper, Kon, and Ruzicka, *J.*, 1934, 124). It (Fig. 1) shows three main regions of absorption (250, 270—300, and 325—350 mμ). The maxima of the three absorption bands of (VII) are shifted to shorter wave-lengths, and the third band is more intense than that of its carbon analogue, in agreement with the findings of Badger, Pearce, and Petit (*J.*, 1951, 3199) for a series of aza-compounds. The ultra-violet spectra of (VI) and (VI*a*) (Fig. 2) have three absorption maxima (225, 250, and 295 mμ).

O

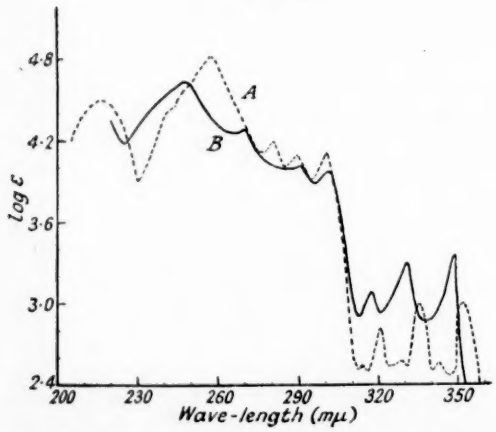
Experimental

M. p.s are uncorrected.

*2-Keto*cyclo*pentanecarboxy-α-naphthalide* (I; R = H).—α-Naphthylamine (14·3 g.) was added during 5 minutes to ethyl 2-keto*cyclo*pentanecarboxylate at 150°. The temperature was raised to 170—180° and the mixture refluxed for 3 minutes. The cooled product was extracted with methanol. On removal of methanol, the oily residue solidified when rubbed with light petroleum (b. p. 40—60°). The *naphthalide*, crystallised from light petroleum–ether, had m. p. 94—95° (15 g.) (Found: C, 75·8; H, 6·5. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 6·0%). The 2 : 4-*dinitrophenylhydrazone* separated from alcohol as yellow crystals, m. p. 236—238° (Found: C, 60·9; H, 4·9. $C_{22}H_{21}O_6N_3$ requires C, 61·0; H, 4·4%).

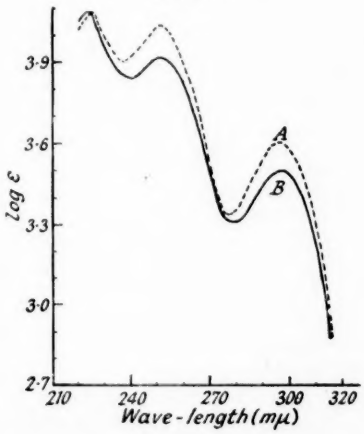
2-α-*Naphthyliminocyclopentanecarboxy-α-naphthalide* (II; R = H).—The solid residue left after extraction with methanol from the above reaction mixture crystallised from ethanol in light yellow needles of the second *naphthalide*, m. p. 162° (4 g.) (Found: C, 82·7; H, 5·9; N, 8·0. $C_{26}H_{22}ON_2$ requires C, 82·5; H, 5·8; N, 7·5%). It gave neither a colour with ferric chloride, nor a crystalline 2 : 4-dinitrophenylhydrazone.

Fig. 1.



A, 15 : 16-*Dihydroxy*cyclo*penta*[a]*phenanthrene* (*Maynecord and Roe*, loc. cit.).
B, 15 : 16-*Dihydro*-11-*aza*cyclo*penta*[a]*phenanthrene*.
Both in ethanol.

Fig. 2.



A, (c–d)trans-*and*, *B*, cis-1 : 2 : 3 : 4 : 11 : 12 : 13 : 14 : 15 : 16-*Decahydro*-11-*aza*cyclo*penta*[a]*phenanthrene*, *in ethanol*.

Ethyl 2-α-*Naphthyliminocyclopentanecarboxylate* (III; R = H).—A mixture of α-naphthylamine (14·3 g.) and ethyl 2-keto*cyclo*pentanecarboxylate (15·6 g.) was kept in a vacuum-desiccator ($CaCl_2$) for a fortnight, yielding a thick liquid, which on seeding and cooling in a refrigerator solidified. The *product* crystallised from methanol as needles, m. p. 73° (Found: C, 77·3; H, 7·1. $C_{18}H_{19}O_2N$ requires C, 76·9; H, 6·7%).

11 : 12 : 15 : 16-*Tetrahydro*-12-*keto*-11-*aza*cyclo*penta*[a]*phenanthrene* (IV; R = H).—2-Keto*cyclo*pentanecarboxy-α-naphthalide (15 g.) was added gradually to cooled concentrated sulphuric acid (25 ml.) with stirring. After the exothermic reaction subsided, the mixture was heated for 15 minutes on a steam-bath, and the deep brown viscous liquid obtained was slowly poured into cold water (1 l.). The precipitated solid *aza-ketone* was washed twice with alcohol and crystallised from 90% acetic acid as needles (11 g.) which sublimed above 250° (Found: C, 81·5; H, 5·7. $C_{16}H_{13}ON$ requires C, 81·7; H, 5·5%).

11 : 12 : 13 : 14 : 15 : 16-*Hexahydro*-12-*keto*-11-*aza*cyclo*penta*[a]*phenanthrene* (V; R = H).—Carbon dioxide was passed into a suspension of (IV; R = H) (10 g.) in absolute alcohol (700 ml.), and sodium hydrogen carbonate (1 g.) then added. Sodium amalgam (700 g.; 4%) was added in portions during 6 hours, and stirring and heating were continued for another 4 hours. The thick pasty mass was filtered hot and the filtrate evaporated to dryness. The solid residue was extracted with benzene (250 ml.), the solvent removed, and the residue on crystallisation

from benzene gave a crystalline *product*, m. p. 180° (7·5 g.) (Found: C, 81·2; H, 6·7. $C_{16}H_{15}ON$ requires C, 81·5; H, 6·4%).

(c–d)cis-1 : 2 : 3 : 4 : 11 : 12 : 13 : 14 : 15 : 16-*Decahydro*-11-*aza*cyclo*penta*[a]*phenanthrene* (VI; R = H).—To a suspension of the previous compound (10 g.) in boiling ethanol (50 ml.), sodium (20 g.) was added, and a further 150 ml. of ethanol were added during the addition of sodium. The mixture, on cooling, solidified and was then dissolved in water. Alcohol was removed in steam. The residue was extracted with ether, the ethereal solution dried (Na_2SO_4), and the solvent removed. A residual thick brown oil solidified when rubbed with light petroleum (b. p. 40—60°). A solution of the crude product on methanol was decolorised with charcoal and filtered. Concentration and cooling yielded the *base*, m. p. 76—77° (Found: C, 84·8; H, 8·9; N, 6·5. $C_{16}H_{21}N$ requires C, 84·6; H, 9·2; N, 6·2%). The *picrate*, m. p. 185° (decomp.), separated from ethanol (Found: C, 58·1; H, 5·4; N, 11·8. $C_{16}H_{21}N,C_6H_3O_7N_3$ requires C, 58·0; H, 5·3; N, 12·3%), and the *benzoyl* derivative, m. p. 160°, from methanol (Found: C, 83·9; H, 7·6; N, 4·3. $C_{23}H_{25}ON$ requires C, 83·4; H, 7·6; N, 4·2%).

15 : 16-*Dihydro*-11-*aza*cyclo*penta*[a]*phenanthrene* (VII; R = H).—Compound (VI; R = H) (1 g.) and selenium (3 g.) were heated at 340—345° for 24 hours in a sealed tube. An ethereal extract of the product was set aside for 2 hours, most of the selenium being deposited. The filtrate therefrom was evaporated to dryness, and the residue dissolved in methanol (charcoal) and filtered. The clear filtrate was concentrated and cooled in ice-water, whereupon the *base*, m. p. 130°, separated (Found: C, 87·3; H, 6·4; N, 6·0. $C_{16}H_{13}N$ requires C, 87·6; H, 6·0; N, 6·4%). The *picrate*, m. p. 237—238°, separated from ethanol (Found: C, 58·9; H, 4·1; N, 12·8. $C_{16}H_{13}N,C_6H_3O_7N_3$ requires C, 59·0; H, 3·6; N, 12·5%). The *methiodide*, obtained by methyl iodide (2 mols.) in acetone at 100° for 24 hours, separated from methanol as yellow needles, m. p. 220° (Found: C, 56·5; H, 4·4. $C_{17}H_{16}NI$ requires C, 56·5; H, 4·4%). This (2 g.) was suspended in water (250 ml.), and 10% aqueous sodium hydroxide (50 ml.) was added gradually; the mixture was left for ½ hour and then extracted with ether, from which (VII) was recovered.

12-*Chloro*-15 : 16-*dihydro*-11-*aza*cyclo*penta*[a]*phenanthrene*.—Compound (IV; R = H) (11·75 g.) and freshly distilled phosphorus oxychloride (12 g.) were refluxed till the whole of the solid dissolved. The hot mixture was poured into ice and water, and set aside for 2 hours. The solid which separated was dissolved in concentrated hydrochloric acid (200 ml.), and the solution filtered. Dilution of the filtrate with water precipitated the hydrochloride, which was decomposed with excess of 30% sodium hydroxide solution. The *base* (4 g.) crystallised from a large volume of ethanol as plates, m. p. 195° (Found: C, 76·0; H, 5·0. $C_{16}H_{12}NCl$ requires C, 75·7; H, 4·7%).

12-*Ethoxy*-15 : 16-*dihydro*-11-*aza*cyclo*penta*[a]*phenanthrene*.—The above chloro-compound (2 g.) in boiling ethanol (200 ml.) was treated with sodium (5 g.). When all the sodium had dissolved, the ethanol was removed in steam and the residue extracted with ether. The extract was dried and evaporated. The *product* (0·8 g.), crystallised from methanol, had m. p. 125° (Found: C, 81·9; H, 6·9. $C_{18}H_{17}ON$ requires C, 82·1; H, 6·5%). 0·7 G. of starting material was recovered.

Reduction of the Chloro-compound.—This compound (1·5 g.), concentrated hydrochloric acid (10 ml.), ethanol (10 ml.), and tin (1·5 g.) were heated together for several hours on the steam-bath, a clear solution being obtained. Alcohol was distilled off. On cooling and dilution of the acid solution a gummy solid was obtained, which was decomposed with excess of 10% sodium hydroxide solution. The base was extracted with ether, the extract dried, and the solvent removed. The residue, crystallised from methanol, had m. p. 76° alone or mixed with (VI; R = H) (Found: C, 85·0; H, 8·8%).

7 : 7a : 9 : 10 : 10a : 11-*Hexahydro*-7-*keto*-11-*aza*cyclo*penta*[b]*phenanthrene* (VIII).—Compound (III; R = H) (14·0 g.) was added to paraffin (250 ml.) at 250° during 5 minutes. Stirring and heating were continued for another 5 minutes. On cooling to 100° the solution was filtered, and the dark brown solid was washed with benzene to remove the last traces of paraffin. The *product* (6·5 g.) separated from 80% acetic acid as colourless crystals which did not melt at 300° (Found: C, 81·7; H, 5·5. $C_{16}H_{13}ON$ requires C, 81·7; H, 5·6%). Its alcoholic solution produced a light reddish-brown colour with ferric chloride.

1 : 2 : 3 : 4 : 11 : 12 : 15 : 16-*Octahydro*-12-*keto*-11-*aza*cyclo*penta*[a]*phenanthrene* (as IV; R = H).—5 : 6 : 7 : 8-Tetrahydro-1-naphthylamine (14·7 g.) (Bamberger, *Ber.*, 1888, **21**, 1786) was condensed with ethyl 2-keto*cyclo*pentanecarboxylate (15·6 g.) as was α-naphthylamine. The *naphthalide* (10 g.) crystallised from ether–light petroleum (b. p. 40—60°) as needles, m. p. 77° (Found: C, 74·2; H, 7·6. $C_{16}H_{19}O_2N$ requires C, 74·7; H, 7·4%). It gave a deep blue

colour with ferric chloride. Ring closure by concentrated sulphuric acid gave a high-melting, sparingly soluble *product* (as IV; R = H), which crystallised from ethanol (Found: C, 80·8; H, 7·6. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·1%).

1 : 2 : 3 : 4 : 11 : 12 : 13 : 14 : 15 : 16-*Decahydro*-12-*keto*-11-*aza*cyclo*penta*[a]*phenanthrene* (as V; R = H).—The above product was reduced by sodium amalgam and boiling alcohol as was (as V; R = H). The *product*, m. p. 135°, crystallised from benzene or alcohol (Found: C, 79·9; H, 8·3. $C_{16}H_{19}ON$ requires C, 79·7; H, 7·9%).

(C–D)trans-1 : 2 : 3 : 4 : 11 : 12 : 13 : 14 : 15 : 16-*Decahydro*-11-*aza*cyclo*pent*[a]*phenanthrene* (VI*a*).—The previous compound was reduced by sodium and boiling alcohol as already described. The secondary *base* had m. p. 60° (from methanol) (Found: C, 84·4; H, 9·6; N, 6·3. $C_{16}H_{17}N$ requires C, 84·6; H, 9·3; N, 6·1%). The *picrate*, m. p. 180° (decomp.), crystallised from alcohol (Found: C, 57·8; H, 5·5. $C_{16}H_{21}N,C_6H_3O_7N_3$ requires C, 58·0; H, 5·3%), and the *benzoyl* derivative, m. p. 120°, from methanol (Found: C, 82·9; H, 7·9. $C_{23}H_{25}ON$ requires C, 83·4; H, 7·6%).

When (VI*a*) was dehydrogenated with selenium, (VII; R = H) (m. p. 129—130°) was produced.

11 : 12 : 15 : 16-*Tetrahydro*-12-*keto*-3-*methoxy*-11-*aza*cyclo*penta*[a]*phenanthrene* (IV; R = OMe).—6-Methoxy-1-naphthylamine (15·7 g.) (Bachman, Wild, and Cole, *J. Amer. Chem. Soc.*, 1940, **62**, 824) was condensed with ethyl 2-keto*cyclo*pentanecarboxylate at 180° as for α-naphthylamine. Ring closure of the crude product by concentrated sulphuric acid produced a high-melting *product* as needles (from 80% acetic acid), which did not melt up to 300° (Found: C, 77·5; H, 6·0. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·7%).

11 : 12 : 13 : 14 : 15 : 16-*Hexahydro*-12-*keto*-3-*methoxy*-11-*aza*cyclo*penta*[a]*phenanthrene* (V; R = OMe).—Reduction of the above compound with sodium amalgam and boiling alcohol gave the *product*, m. p. 212° (from benzene) (Found: C, 76·7; H, 6·9. $C_{17}H_{17}O_2N$ requires C, 76·4; H, 6·4%). Reduction of this with (*a*) sodium and alcohol, (*b*) hydrogen in the presence of Adams's catalyst, or (*c*) lithium aluminium hydride in tetrahydrofuran proved unsuccessful and the original material in (*b*) and (*c*) was obtained unchanged, whereas a tar was obtained in (*a*).

N-2′-*Cyanoethylamino*-α-*naphthylamine*.—α-Naphthylamine (14·3 g.), acrylonitrile (7·5 g.), and glacial acetic acid (1 g.) were heated in a sealed tube for 16 hours at 120—125°. The *product* was distilled and the fraction, b. p. 154—155°/0·5 mm., a light yellow viscous mass, solidified overnight. Crystallised from methanol it had m. p. 71—72° (10 g.) (Found: C, 79·7; H, 6·3; N, 13·9. $C_{13}H_{12}N_2$ requires C, 80·0; H, 6·1; N, 14·3%). Hydrolysis with alcoholic potassium hydroxide on the steam bath produced the *carboxylic acid*, m. p. 145—146° (Found: C, 72·4; H, 6·4. $C_{13}H_{13}O_2N$ requires C, 72·5; H, 6·1%).

Methylacrylonitrile.—Methods of preparing this substance from acetone cyanohydrin have been described (Henry, *Chem. Zentr.*, 1898, **11**, 662; Buris, Jones, and Ritchie, *J.*, 1935, 716) but we did not find them convenient. We obtained better yields by dehydration of methylacrylamide (*Org. Synth.*, **29**, 61). Methylacrylamide (8·5 g.) and phosphoric oxide (7·0 g.) were heated in a distilling flask. A colourless liquid (5·0 g.), b. p. 85—95°, was collected, which was washed with sodium carbonate solution, dried (P_2O_5), and distilled. 4·0 g. of colourless liquid, b. p. 90—91°, were obtained. Henry (*loc. cit.*) recorded b. p. 90—92°.

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41. *The Chemistry of the Platinum Metals. Part II.* Fluoropalladates and Fluoroplatinates.*

By A. G. Sharpe.

The compounds K_2PdF_6, Rb_2PdF_6, Cs_2PdF_6, Rb_2PtF_6, and Cs_2PtF_6 are obtained by interaction of the corresponding complex chlorides and bromine trifluoride. The ions PdF_6^{2-} and PtF_6^{2-} are similar in size and magnetic properties, but PdF_6^{2-} differs from PtF_6^{2-} in being immediately hydrolysed by water. Rb_2PtF_6 and Cs_2PtF_6 are isomorphous with K_2PtF_6 and hence with K_2GeF_6; Cs_2PdF_6 has the K_2PtCl_6 structure. The occurrence of the K_2GeF_6 and K_2PtCl_6 structures among complex halides is discussed.

The chemistry of potassium hexafluoroplatinate was described in some detail in Part I,* where evidence was presented to show that reactions of the PtF_6^{2-} ion with water and iodide ion are thermodynamically possible but extremely slow. It was also shown that bromine trifluoride converts palladium dichloride into the trifluoride, and potassium tetrachloropalladite into a complex fluoride which is rapidly decomposed by water. At that time, it was assumed that the complex would be a derivative of palladium trifluoride. No definite compound was obtained, however; and it has since become apparent that at the temperatures (200—280°) employed for the removal of bromine trifluoride from the complex, some decomposition had taken place.

Further investigation showed that if potassium tetrachloropalladite or hexachloropalladate is treated with bromine trifluoride and the product of the reaction is heated to constant weight at 150°, the pale yellow residue has the composition $K_2PdF_6,0{\cdot}1BrF_3$. This residue is diamagnetic, and therefore resembles potassium hexafluoroplatinate (Nyholm and Sharpe, *J.*, 1952, 3579) and potassium hexafluoronickelate, K_2NiF_6 (Hoppe, *Angew. Chem.*, 1950, **62**, 339). Rubidium and cæsium chloropalladates and bromine trifluoride yield, under similar conditions, the pure fluoropalladates Rb_2PdF_6 and Cs_2PdF_6. The fluoropalladates are immediately decomposed by water: $PdF_6^{2-} + 2H_2O = PdO_2 + 4H^+ + 6F^-$. Since palladium dioxide is not redissolved by hot concentrated hydrofluoric acid (though it is readily soluble in hydrochloric acid), the hydrolysis appears to be irreversible. The oxidation state of the palladium is shown to remain constant by the formation of potassium hexachloropalladate if the precipitated oxide is filtered off, dissolved in hydrochloric acid, and added to a solution of potassium chloride.

It is shown below that the PdF_6^{2-} and PtF_6^{2-} ions are of about equal size, and since the bond type in these ions (as deduced from their magnetic susceptibilities, which indicate that the 4*d* and 5*d* orbitals respectively are all full) is the same, comparison of their rates of reaction with water is of some interest in connection with theories of the mechanism of substitution in complex ions, a subject which has recently been extensively reviewed by Taube (*Chem. Reviews*, 1952, **50**, 69), who considered a series of complex ions in which the central atoms had the same charge and co-ordination number (six) and differed only slightly in size. Since, for replacement of fluorine or chlorine in the complex ions by water, the rates vary widely, he deduced that an electronic factor must be involved, and concluded that an empty *d* orbital in the outermost but one shell is usually associated with rapid substitution. For attack on PdF_6^{2-} or PtF_6^{2-} with co-ordination on to the central atom as the rate-determining step, steric and electronic factors should be the same for both ions; and even consideration of the known higher valencies of metals of the third transition series appears to favour substitution in the platinum-containing ion, provided that the mechanism of substitution in the two ions is the same. The experimental data appear to show that this last condition is not fulfilled, and that PdF_6^{2-} (and presumably also NiF_6^{2-}) hydrolyse by a mechanism different from that for PtF_6^{-2}. Dissociation of the complex ion, rather than substitution, may perhaps be the governing process for ions of high oxidation states such as Ni^{IV} and Pd^{IV}. It should be noted that the rate-determining step for hydrolysis of

* *J.*, 1950, 3444, is considered Part I of this series.

the SiF_6^{2-} ion is the first-order process $SiF_6^{2-} \longrightarrow SiF_4 + 2F^-$ (Hudleston and Bassett, *J.*, 1921, **119**, 403; Rees and Hudleston, *J.*, 1936, 1334), and that substitutions such as $PtF_6^{2-} + 6I^- \longrightarrow PtI_6^{2-} + 6F^-$, which proceed at measurable speed only in the presence of hydrogen ions, have orders higher than unity. The speed of hydrolysis of PdF_6^{2-} unfortunately makes determination of the order of reaction almost impossible. This difference between PdF_6^{2-} and PtF_6^{2-} emphasizes the need for caution in classifying substitution processes until more is known of the mechanisms, as distinct from the rates, of such reactions.

The structure of potassium hexafluoroplatinate has recently been described by Mellor and Stephenson (*Austral. J. Sci. Res.*, 1951, **4**, *A*, 406): K_2PtF_6 is isomorphous with K_2GeF_6 (Hoard and Vincent, *J. Amer. Chem. Soc.*, 1939, **61**, 2849), the dimensions of the hexagonal unit cells being respectively $a = 5{\cdot}76$, $c = 4{\cdot}64$, and $a = 5{\cdot}62$, $c = 4{\cdot}65$ Å. The rubidium and cæsium salts have now been prepared by the action of bromine trifluoride on the chloroplatinates. A preliminary examination of their structures by the powder method indicates that both are isomorphous with K_2PtF_6: for Rb_2PtF_6, $a = 5{\cdot}96$, $c = 4{\cdot}83$ Å; for Cs_2PtF_6, $a = 6{\cdot}22$, $c = 5{\cdot}01$ Å. The structure of Rb_2PdF_6 has not been elucidated, but Cs_2PdF_6 is isomorphous with K_2PtCl_6, with $a = 9{\cdot}01$ Å. For Cs_2GeF_6, which also has this structure, Wyckoff and Müller (*Amer. J. Sci.*, 1927, **13**, 347) reported $a = 8{\cdot}99$ Å. From the lattice constants of K_2GeF_6, K_2PtF_6, Cs_2GeF_6, and Cs_2PdF_6 we may therefore reasonably conclude that the ions GeF_6^{2-}, PdF_6^{2-}, and PtF_6^{2-} are similar in shape and size.

In K_2GeF_6 (Hoard and Vincent, *loc. cit.*) each K^+ ion has nine F at 2·85 Å and three F at 3·01 Å: and the environment of the K^+ ions in the isomorphous K_2TiF_6 (Siegel, *Acta Cryst.*, 1952, **5**, 683) is also unsymmetrical. In Rb_2GeF_6 (which is also hexagonal) each Rb^+ ion has twelve almost equidistant F neighbours (Vincent and Hoard, *J. Amer. Chem. Soc.*, 1942, **64**, 1233); in Cs_2GeF_6 (cubic) the twelve Cs–F distances are, so far as is known, identical. This variation has been generally attributed to the relatively small size of the K^+ ion (see, *e.g.*, Wells, "Structural Inorganic Chemistry," Oxford, 1950), but this explanation ceases to be convincing when we recall that in K_2PtBr_6 the K^+ ion can have twelve much larger Br atoms as nearest neighbours. Furthermore, in the series K_2PtF_6, K_2PtCl_6, K_2PtBr_6, only the salt with the smallest anion is non-cubic, and, despite the closeness in unit cell dimensions of K_2PtF_6 and K_2GeF_6, Mellor and Stephenson attribute the structure of K_2PtF_6 to the relative smallness of the *anion*.

The relation of the K_2PtCl_6 structure to cubic close-packing is admirably discussed by Wells (*op. cit.*), who shows that K_2SiF_6 (which has this structure) may be described from the point of view of pure geometry as a lattice of cubic close-packed layers of suitably arranged halogen and alkali-metal atoms in numerical ratio of 3 : 1, with one half of the octahedral holes occupied by silicon atoms. Wells and Hoard and Vincent have also drawn attention to the fact that in K_2GeF_6 and Rb_2GeF_6 the packing of alkali-metal and fluorine atoms approximates to hexagonal close-packing. It is now suggested that in addition to the cubic K_2PtCl_6 structure for complex halides of general formula A_2BX_6 (where A is a large cation such as K, Rb, Cs, or NH_4) there is an ideal hexagonal structure in which the packing of the layers containing the A and X atoms is hexagonal (instead of cubic) close-packing. There is, of course, no reason why there should not be some deviation from the ideal structure, such as is found in K_2GeF_6 and K_2TiF_6; but it is suggested that such deviations are comparatively unimportant. If this hypothesis is accepted, there should be little difference in energy between the cubic and hexagonal structures, and the significance of their distribution should be something like that of the distribution of cubic and hexagonal close-packing in the structures of metals.

In spite of the much greater ionic radius of cæsium, K_2PtF_6 and Cs_2PtF_6 are isomorphous; Cs_2PdF_6 and Cs_2PtF_6 are not isomorphous, although the octahedral radii of Pd^{IV} and Pt^{IV} are equal; in the series K_2SiF_6 (dimorphic, cubic, or hexagonal), K_2GeF_6 (hexagonal), K_2PtF_6 (hexagonal), K_2PtCl_6 (cubic), there is no regular variation in structure with increasing anion size. These facts are quite incapable of simple explanation based solely on radius ratio effects, but present no difficulty if we accept the possibility of two ideal structures differing only slightly in energy content, and in which the co-ordination numbers of the atoms are identical.

Hitherto, the K_2GeF_6 structure for complex salts A_2BX_6 has been identified by *X*-ray methods only in one form of $(NH_4)_2SiF_6$ (Gossner and Kraus, *Z. Krist.*, 1934, **88**, 223), $(NH_4)_2GeF_6$ (Hoard and Vincent, *loc. cit.*), Cs_2PuCl_6 (Zachariasen, *Acta Cryst.*, 1948, **1**, 268), and the compounds mentioned above. A systematic search should, however, reveal that it is much more common than has formerly been supposed; the results of such a search will be reported in a later communication.

Experimental

Reaction involving bromine trifluoride and analyses of palladium and platinum compounds were carried out by methods described or referred to in Part I.

Hexafluoropalladates.—The sparingly soluble hexachloropalladates of potassium, rubidium, and cæsium were made by warming solutions of the tetrachloropalladites with sodium chlorate and hydrochloric acid. The complex chlorides were treated with bromine trifluoride, and the reaction products were heated to constant weight at 150°.

Rubidium and cæsium hexafluoropalladates were thus obtained free from chlorine or bromine, but attempts to obtain the potassium salt free from bromine were unsuccessful; heating above 200° produced decomposition (Found, for Rb salt: Pd, 28·0; F, 28·0. Rb_2PdF_6 requires Pd, 27·4; F, 29·1%. Found, for Cs salt: Pd, 21·7; F, 23·8. Cs_2PdF_6 requires Pd, 21·9; F, 23·4%. Found, for K salt: Pd, 34·5; F, 37·9; Br, 2·5. Calc. for K_2PdF_6: Pd, 35·7; F, 38·2%; Br, nil). The analytical data given for the potassium salt (typical of several preparations) correspond with an approximate composition $K_2PdF_6,0{\cdot}1BrF_3$, indicating slight solvolysis; the instability of the fluoropalladates unfortunately precludes further purification.

The three hexafluoropalladates are all pale yellow salts soluble in hot, sparingly soluble in cold, bromine trifluoride. They are immediately hydrolysed by cold water, and rapidly turn brown on exposure to the atmosphere. Treatment with concentrated hydrochloric acid at once produces the hexachloropalladates. The magnetic susceptibility of the (slightly impure) potassium salt at 20° is $-0{\cdot}23 \times 10^{-6}$ c.g.s. units.

X-Ray powder photographs were taken with Cu-K_α radiation; samples were filled into Pyrex capillaries by using the " dry box " technique, and the capillaries were at once sealed off with warm picein wax. All of the lines on the photograph of the cæsium salt could be indexed on the basis of a face-centred cubic unit cell with $a = 9{\cdot}01$ Å. The relative intensities of the lines (visually estimated) corresponded with those on the powder pattern of a sample of Cs_2PdCl_6 [Found: $a = 10{\cdot}17$ Å. Ketelaar and van Walsem (*Rec. Trav. chim.*, 1938, **57**, 964) give $a = 10{\cdot}16$ Å] in which fluorine is replaced by another relatively light element; Cs_2PdF_6 and Cs_2PdCl_6 are therefore isomorphous. The powder pattern of the rubidium salt could not be indexed.

Hexafluoroplatinates.—*Rubidium* and *cæsium hexafluoroplatinates* were made by interaction of the chloroplatinates and bromine trifluoride, followed by heating of the residue at 200°. The pale yellow, very sparingly soluble salts were recrystallised from water (Found, for Rb salt: Pt, 40·0. Rb_2PtF_6 requires Pt, 40·7%. Found, for Cs salt: Pt, 34·4. Cs_2PtF_6 requires Pt, 34·4%). Reactions of these salts with potassium iodide and with hydrochloric acid are exactly like those of the potassium salt, described in Part I.

X-Ray powder photographs of the potassium, rubidium, and cæsium salts showed similar patterns, all of which could be indexed on the basis of hexagonal unit cells. For K_2PtF_6, values $a = 5{\cdot}76$, $c = 4{\cdot}64$ Å were found, in agreement with Mellor and Stephenson; cell constants for Rb_2PtF_6 and Cs_2PtF_6 are quoted above.

Grateful acknowledgment is made to Professor R. S. Nyholm for a determination of magnetic susceptibility, and to Messrs. Johnson, Matthey, and Company, Limited, for the loan of compounds of palladium and platinum.

University Chemical Laboratory, Cambridge. [*Received, October 2nd*, 1952.]

42. *Melanin and Its Precursors. Part VI.* Further Syntheses of 5 : 6-Dihydroxyindole and its Derivatives.*

By JOHN HARLEY-MASON.

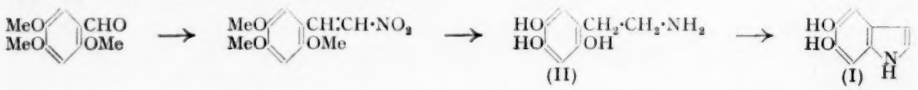
5 : 6-Dihydroxyindole is obtained in good yield by autoxidation of 2-(6-amino-3 : 4-dihydroxyphenyl)ethylamine and by ferricyanide oxidation of 2-(2 : 4 : 5-trihydroxyphenyl)ethylamine.

5 : 6-Dihydroxy-2-methyl- and -2 : 3-dimethyl-indole are readily obtained by demethylation of the corresponding 5 : 6-dimethoxyindoles with hydrobromic acid. In the reduction of 4 : 5-dimethoxy-2-nitro-1-2′-nitropropenylbenzene a 3 : 3′-di-indolyl derivative is obtained in addition to the expected 5 : 6-dimethoxy-2-methylindole.

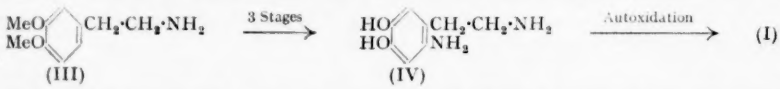
Ferricyanide oxidation of *N*-3 : 4-dihydroxybenzyl-2-(3 : 4-dihydroxyphenyl)ethylamine gives 1-(3 : 4-dihydroxybenzyl)-5 : 6-dihydroxyindole, but attempts to oxidise this further to a tetracyclic phenanthridine derivative were unsuccessful.

METHODS at present available for the synthesis of 5 : 6-dihydroxyindole (I) include the oxidation of 3 : 4-dihydroxyphenylalanine and subsequent rearrangement of the quinonoid-product (Bu'Lock and Harley-Mason, *J.*, 1951, 2248), and the reduction of 4 : 5-diacetoxy-β : 2-dinitrostyrene and subsequent hydrolysis of the diacetoxyindole thus obtained (Beer, Clarke, Khorana, and Robertson, *J.*, 1948, 2223). The first method gives low and erratic yields whilst the second requires as starting product 6-nitroprotocatechualdehyde which is difficult to prepare on a considerable scale. Accordingly a search was made for a more convenient synthesis.

It had earlier been shown (Part V, *loc. cit.*) that oxidation of 2-(2 : 5-dihydroxyphenyl)-ethylamine gave 5-hydroxyindole in good yield and this approach has now been extended to the oxidation of 2-(2 : 4 : 5-trihydroxyphenyl)ethylamine (II), readily obtained from 2 : 4 : 5-trimethoxybenzaldehyde *via* the nitrostyrene. On oxidation with potassium ferricyanide (II) gave a good yield of (I).



The starting product in this case is, however, not commercially available and an alternative rather similar synthesis was then developed starting from the readily available 2-(3 : 4-dimethoxyphenyl)ethylamine (III). This material on nitration gave the 4 : 5-dimethoxy-2-nitro-derivative which was reduced catalytically to the corresponding amino-compound. On demethylation this afforded 2-(2-amino-4 : 5-dihydroxyphenyl)ethylamine (IV) as dihydrobromide, the overall yield up to this point being 70%. The diamine, on



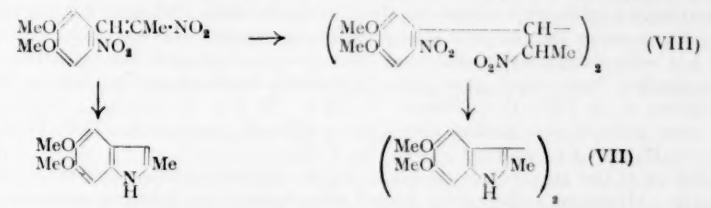
liberation from its salt, which was quite stable, autoxidised in aqueous solution extremely readily to give (I), the reaction presumably proceeding *via* a quinone-imine intermediate and resembling the synthesis described above except that ammonia instead of water is liberated in the cyclisation. Quite good yields were obtained and the synthesis is the simplest available for 5 : 6-dihydroxyindole. Oxidation of (IV) with potassium ferricyanide was unsatisfactory owing to the formation of a very sparingly soluble amine ferricyanide.

One further synthesis of (I) was examined : bromination of 2-(3 : 4-dimethoxyphenyl)-ethylamine gave the bromo-derivative which was then demethylated to 2-(2-bromo-4 : 5-dihydroxyphenyl)ethylamine. Oxidation with potassium ferricyanide gave 5 : 6-dihydr-

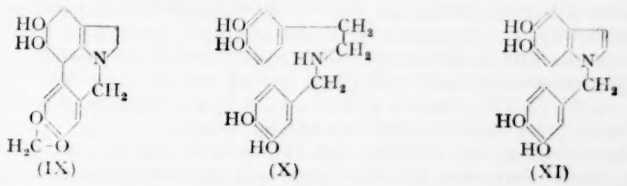
* Part V, *J.*, 1952, 2525.

oxyindole by cyclisation with elimination of hydrogen bromide, but much amorphous insoluble by-product was formed and the yield was very low.

5 : 6-Dihydroxy-2 : 3-dimethylindole was prepared by Beer, McGrath, Robertson, and Woodier (*J.*, 1949, 2061) by demethylation of the corresponding dimethoxy-compound with aluminium bromide. It has now been found that demethylation is effected more easily by short boiling with hydrobromic acid. 5 : 6-Dihydroxy-2-methylindole was similarly obtained from 5 : 6-dimethoxy-2-methylindole (V). The latter, which had earlier been obtained by Lions (*J. Proc. Roy. Soc. N.S.W.*, 1930, **63**, 168), was prepared more conveniently by reduction of 4 : 5-dimethoxy-2-nitro-1-2′-nitropropenylbenzene (VI) with iron powder and acetic acid (cf. Beer *et al.*, *loc. cit.*). From this reduction a



considerable amount of a sparingly soluble by-product was obtained in addition to (V) : analysis indicated a molecular formula approximately twice that of (V), so the compound is regarded as 5 : 6 : 5′ : 6′-tetramethoxy-2 : 2′-dimethyl-3 : 3′-di-indolyl (VII), arising from reduction of the dimeric intermediate (VIII). It has been shown (Sonn and Schellenberg, *Ber.*, 1917, **50**, 1513; Kohler and Drake, *J. Amer. Chem. Soc.*, 1923, **45**, 1281) that hydrogenation of β-nitrostyrenes over platinum affords " hydrodimers " (1 : 4-dinitro-2 : 3-diarylbutanes) of the type of (VIII), and it seems probable that a reductive dimerisation of this kind occurs to some extent in the reduction of (VI) described above. Hydrobromic acid caused extensive decomposition of (VII), with a small amount of 5 : 6-dihydroxy-2-methylindole as sole isolable product.



A further and more complex case of 5 : 6-dihydroxyindole formation was next examined. The structure (IX) has been advanced for the alkaloid lycorine (isolated from several species of *Amaryllidacaea*) on the basis of degradative studies (Kondo and Uyeo, *Ber.*, 1937, **70**, 1087, 1094; 1938, **71**, 1529: Kondo and Katsura, *Ber.*, 1939, **72**, 2083; 1940, **73**, 112, 1424). An attempt was made to synthesise a tetracyclic structure of this kind, but with only partial success. The amine (X) was prepared by a method similar to that of Buck (*J. Amer. Chem. Soc.*, 1931, **53**, 2192), and oxidised with potassium ferricyanide. The product, obtained in 40% yield was, however, 1-(3 : 4-dihydroxybenzyl)-5 : 6-dihydroxyindole (XI) and attempts at further oxidation, to the tetracyclic system of lycorine, were unsuccessful.

Experimental.

2-(2 : 4 : 5-*Trihydroxyphenyl*)*ethylamine*.—2 : 4 : 5-Trimethoxybenzaldehyde (4 g.), nitromethane (1·5 g.), and ammonium acetate (1 g.) were refluxed in acetic acid (30 c.c.) for 3 hours. After cooling, dilution with water precipitated the product which was recrystallised from ethanol. 2 : 4 : 5-*Trimethoxy*-β-*nitrostyrene* (3·5 g.) formed orange-red prisms, m. p. 131—132° (Found : C, 55·0; H, 5·4. $C_{11}H_{13}O_5N$ requires C, 55·1; H, 5·4%).

The nitrostyrene (3 g.) was extracted (Soxhlet) into a solution of lithium aluminium hydride (2 g.) in ether (200 c.c.), boiling being continued for 6 hours. The resulting suspension was decomposed with a concentrated solution of sodium potassium tartrate, the ethereal layer

separated and dried (KOH), and the solvent removed, leaving 2-(2 : 4 : 5-trimethoxyphenyl)-ethylamine as a waxy solid. A portion was converted into the *hydrochloride*, plates (from ethanol–ether), m. p. 187—188° (decomp.) (Found: C, 53·1; H, 7·4. $C_{11}H_{18}O_3NCl$ requires C, 53·3; H, 7·3%).

The amine (2 g.) was refluxed for 1 hour with hydrobromic acid (*d* 1·49; 15 c.c.). On cooling, 2-(2 : 4 : 5-*trihydroxyphenyl*)*ethylamine hydrobromide* separated and recrystallised from ethanol–ether, forming needles, m. p. 216—218° (Found, on a sample dried at 80°/0·1 mm.: C, 38·9; H, 5·0. $C_8H_{12}O_3NBr$ requires C, 38·4; H, 4·8%).

2-(2-*Amino*-4 : 5-*dihydroxyphenyl*)*ethylamine*.—An ice-cold solution of 3 : 4-dimethoxyphenylethylamine (5 g.) in water (15 c.c.) and concentrated nitric acid (5 c.c.) was added slowly with stirring to nitric acid (free from nitrous acid; *d* 1·4; 35 c.c.), at 10—15° (cooling). Separation of the sparingly soluble nitro-amine nitrate soon commenced, and after 2 hours the mixture was diluted with ice-water and the crystalline precipitate collected. It was dissolved in boiling water, basified hot with sodium hydroxide, and then cooled, whereupon the nitro-amine crystallised. Recrystallisation from water gave 2-(4 : 5-*dimethoxy*-2-*nitrophenyl*)*ethylamine* (4·8 g.) as pale yellow plates, m. p. 110—111° (Found: C, 53·2; H, 6·2. $C_{10}H_{14}O_4N_2$ requires C, 53·0; H, 6·2%). The *hydrochloride* formed plates (from ethanol), m. p. 228—230° (Found: C, 45·25; H, 5·9. $C_{10}H_{15}O_4N_2Cl$ requires C, 45·6; H, 5·7%).

A solution of the amine (5 g.) in ethanol (50 c.c.) was hydrogenated over Raney nickel at 50°/50 atm. Hydrogen chloride was passed into the resulting solution, whereupon the diamine dihydrochloride was precipitated, and a further quantity was obtained by addition of ether to the filtrate. 2-(2-*Amino*-4 : 5-*dimethoxyphenyl*)*ethylamine dihydrochloride* formed plates (from 95% ethanol), m. p. 247—248° (decomp.) (Found: C, 44·2; H, 6·8; N, 10·4. $C_{10}H_{18}O_4N_2Cl_2$ requires C, 44·6; H, 6·7; N, 10·4%).

The dihydrochloride (4 g.) was refluxed for an hour with hydrobromic acid (*d* 1·49; 30 c.c.). On cooling, 2-(2-*amino*-4 : 5-*dihydroxyphenyl*)*ethylamine dihydrobromide* crystallised and was recrystallised from ethanol–ether, forming plates, m. p. 239—241° (decomp.) (Found: C, 28·8; H, 4·4. $C_8H_{14}O_4N_2Br_2$ requires C, 29·0; H, 4·1%). Addition of ammonia to a concentrated aqueous solution precipitated the crystalline free base but this proved too unstable for characterisation.

2-(2-*Bromo*-4 : 5-*dihydroxyphenyl*)*ethylamine*.—To a cooled solution of 3 : 4-dimethoxyphenylethylamine (5·4 g.) in acetic acid (20 c.c.), bromine (4·8 g.) in acetic acid (15 c.c.) was added slowly with stirring. Separation of the product soon commenced, and after being kept overnight the crystals were collected and twice recrystallised from ethanol. 2-(2-*Bromo*-4 : 5-*dimethoxyphenyl*)*ethylamine hydrobromide* (7 g.) formed prisms, m. p. 202—204° (Found: C, 35·6; H, 4·5. $C_{10}H_{11}O_2NBr_2$ requires C, 35·1; H, 4·4%). Addition of sodium hydroxide to an aqueous solution precipitated the free base as white plates.

The hydrobromide (5 g.) was refluxed with hydrobromic acid (*d* 1·49; 35 c.c.) for 45 mins. (longer boiling caused darkening and decomposition), and the excess of acid removed under reduced pressure. The dihydroxy-amine hydrobromide formed a pale yellow glass.

5 : 6-*Dihydroxyindole*.—(*a*) To a solution of 2 : 4 : 5-trihydroxyphenylethylamine hydrobromide (1·0 g.) in water (25 c.c.), potassium ferricyanide (2·5 g.) and sodium hydrogen carbonate (1·0 g.) in water (25 c.c.) were added with stirring. The intensely red solution was kept under hydrogen for 24 hours, the colour changing to dirty brown, and was then extracted with ethyl acetate (3 × 30 c.c.). The extract was dried (Na_2SO_4), the solvent removed under hydrogen, and the residue sublimed at 150°/0·01 mm., giving 5 : 6-dihydroxyindole, m. p. 140° (decomp.) (0·3 g., 50%).

(*b*) A rapid stream of air was passed through a solution of 2-(2-amino-4 : 5-dihydroxyphenyl)-ethylamine dihydrobromide (1·7 g.) and sodium hydrogen carbonate (0·5 g.) in water (75 c.c.), which rapidly became deep violet-red as oxidation proceeded. When the colour had attained a maximum intensity (about 10 mins.) the current of air was stopped, the solution kept under hydrogen for 12 hours and then extracted with ethyl acetate (3 × 30 c.c.), and the extract worked up as in (*a*). In several experiments the yield of 5 : 6-dihydroxyindole varied from 0·25 to 0·4 g. (30—50%). The duration of the oxidation is critical, and, if it is continued too long, much 5 : 6-dihydroxyindole is further oxidised.

(*c*) To a solution of 2-(2-bromo-4 : 5-dihydroxyphenyl)ethylamine hydrobromide (1·6 g.) in water (30 c.c.), potassium ferricyanide (3·2 g.) and sodium hydrogen carbonate (1·7 g.) in water (30 c.c.) were added slowly with stirring. A voluminous dark blue-black precipitate was then filtered off. The filtrate was extracted with ethyl acetate and worked up as above, giving 5 : 6-dihydroxyindole (0·06 g., 8%).

5 : 6-*Dimethoxy*-2-*methylindole*.—To a solution of 3 : 4-dimethoxy-1-2′-nitropropenylbenzene (Bu'Lock and Harley-Mason, *loc. cit.*) (5 g.) in acetic acid (35 c.c.), concentrated nitric acid (*d* 1·5; 15 c.c.) was added dropwise with stirring, at < 15° (cooling). After an hour the mixture was poured into water and the precipitate recrystallised from ethanol. **4 : 5-*Dimethoxy*-2-*nitro*-1-2′-*nitropropenylbenzene*** (VI) (5 g.) formed yellow plates, m. p. 133° (Found: C, 49·0; H, 4·6. $C_{11}H_{12}O_6N_2$ requires C, 49·3; H, 4·5%).

To a solution of the dinitro-compound (4 g.) in hot (not boiling) acetic acid (100 c.c.) and water (20 c.c.), iron powder (20 g.) was added in small portions. The mixture boiled vigorously after each addition, and when the reaction had subsided the solution was decanted as far as possible from undissolved residue and poured into water (500 c.c.). It was then extracted with ethyl acetate (4 × 100 c.c.), and the extract washed free from acetic acid with sodium hydrogen carbonate solution, dried, concentrated to 25 c.c., and kept at 0°. The pale brown crystalline solid (A) which had separated was filtered off and the filtrate diluted with light petroleum (b. p. 80—100°). **5 : 6-Dimethoxy-2-methylindole** (1·8 g.) crystallised gradually at 0°, and was recrystallised (charcoal) from benzene–light petroleum, giving plates, m. p. 91°. Lions (*loc. cit.*) gives m. p. 91°.

The solid (A) above was recrystallised twice (charcoal) from acetone, giving **5 : 6 : 5′ : 6′-*tetramethoxy*-2 : 2′-*dimethyl*-3 : 3′-*di-indolyl*** (VII) (0·8 g.) as white plates, m. p. 256—258° (Found: C, 69·9; H, 6·4; N, 7·4%; *M* (Rast), 365. $C_{22}H_{24}O_4N_2$ requires C, 69·5; H, 6·3; N, 7·35%; *M*, 380]. The product is sparingly soluble in the common organic solvents; with alcoholic hydrogen chloride (slowly) or Ehrlich's reagent a blue colour develops.

5 : 6-*Dihydroxy*-2-*methyl*- *and* -2 : 3-*dimethyl-indole*.—5 : 6-Dimethoxy-2-methylindole (0·5 g.) was refluxed for an hour with hydrobromic acid (*d*, 1·49; 10 c.c.). The solution, which had darkened considerably, was cooled, diluted with water (50 c.c.), and extracted with ethyl acetate (3 × 30 c.c.). The extract was dried (Na_2SO_4) and the solvent removed under hydrogen. Sublimation of the residue at 160°/0·005 mm. gave 5 : 6-dihydroxy-2-methylindole (0·25 g.), darkening at 180° and decomposing above this temperature as recorded by Beer *et al.* (*loc. cit.*) (Found: C, 66·0; H, 5·6. Calc. for $C_9H_9O_2N$: C, 66·3; H, 5·5%).

Similar treatment of 5 : 6-dimethoxy-2 : 3-dimethylindole gave the corresponding 5 : 6-dihydroxyindole, m. p. *ca.* 190° (decomp.).

1-3 : 4-*Dihydroxybenzyl*-5 : 6-*dihydroxyindole* (XI).—A mixture of veratraldehyde (8·4 g.) and 2-(3 : 4-dimethoxyphenyl)ethylamine (9 g.) was warmed at 100° for 0·5 hour and the resulting Schiff's base dissolved in ethanol (150 c.c.) and hydrogenated at 50°/50 atm. over Raney nickel. Hydrogen chloride was passed into the resulting solution and after addition of ether the precipitated amine hydrochloride (16 g.) was collected. The hydrochloride (10 g.) was demethylated by 2 hours' refluxing with hydrobromic acid (*d* 1·49; 80 c.c.). On cooling, ***N*-3 : 4-**dihydroxybenzyl-2-(3 : 4-dihydroxyphenyl)ethylamine hydrobromide (8·5 g.) crystallised.

To a solution of the hydrobromide (3·56 g.) in water (500 c.c.), potassium ferricyanide (13·1 g.) and sodium hydrogen carbonate (4·2 g.) in water (300 c.c.) were added during an hour with vigorous stirring. The solution became reddish-brown and a brown amorphous precipitate separated. Stirring was continued for a further hour and the precipitate was then filtered off and the filtrate extracted with ethyl acetate (4 × 100 c.c.). The extract was dried (Na_2SO_4) and concentrated to 20 c.c. Light petroleum (b. p. 60—80°; 20 c.c.) was added and the amorphous precipitate formed was filtered off. To the warmed filtrate, light petroleum (b. p. 40—60°; 100 c.c.) was added and, after storage overnight at 0°, the crystalline product was collected and recrystallised from water (20 c.c.). Dried at 70° in a vacuum, **N-3 : 4-*dihydroxybenzyl*-5 : 6-*dihydroxyindole*** (0·8 g.) formed prisms, m. p. 143—145°, sparingly soluble in cold water, readily soluble in the common organic solvents, and giving an intense purple colour with Ehrlich's reagent (Found: C, 66·15; H, 5·0; N, 5·2. $C_{15}H_{13}O_4N$ requires C, 66·2; H, 4·7; N, 5·2%). Acetylation (acetic anhydride–pyridine; 24 hours in the cold) gave a ***tetra-acetate*** which formed prisms (from ethanol), m. p. 194—195° (Found: C, 63·2; H, 4·9. $C_{23}H_{21}O_8N$ requires C, 63·0; H, 4·8%).

Attempts at further oxidation using potassium ferricyanide, ferric acetate or chloranil all led to intractable insoluble products, and no definite product could be isolated from the precipitate discarded in the course of the preparation.

The author thanks Mr. A. H. Jackson for the preparation of 2 : 4 : 5-trimethoxybenzaldehyde.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October 6th*, 1952.]

43. *Solutions in Sulphuric Acid. Part IX.* The Electrical Conductivity of the Water–Sulphur Trioxide System in the Region of the Composition of Sulphuric Acid.*

By R. J. Gillespie and S. Wasif.

The electrical conductivity of the water–sulphur trioxide system for compositions in the neighbourhood of sulphuric acid has been re-investigated at 25°. A few measurements have also been made at 10·4°. The results are discussed and compared with those of earlier investigations.

The work described in this and the following three papers represents a continuation of a detailed investigation of solutions in sulphuric acid, the first part of which was carried out by the cryoscopic method (Parts I—VIII; *J.*, 1950, 2473—2537 and 2997).

The conductivity of the water–sulphur trioxide system in the region of the composition of sulphuric acid was first investigated by Kohlrausch (*Wied. Ann.*, 1882, **17**, 69), who found a minimum conductivity at a composition of 99·75% of H_2SO_4 and 0·25% of H_2O at 25°. Later Knietsch (*Ber.*, 1901, **34**, 4107) found a minimum conductivity at 99·9% of H_2SO_4 and 0·1% of H_2O at 25°. Hantzsch (*Z. physikal. Chem.*, 1907, **61**, 257) was the first to make a systematic study by means of both conductivity and cryoscopic measurements of water, sulphur trioxide, and other solutes in sulphuric acid and he found a minimum conductivity of 0·0098 ohm^{-1} $cm.^{-1}$ at the composition 100% of H_2SO_4 at 25°. Further measurements were reported by Lichty (*J. Amer. Chem. Soc.*, 1908, **30**, 1834), who found a minimum conductivity of 0·01041 ohm^{-1} $cm.^{-1}$ at the composition of sulphuric acid at 25°. Bergius (*Z. physikal. Chem.*, 1910, **72**, 338) repeated and extended Hantzsch's work and found a minimum conductivity of 0·0097 ohm^{-1} $cm.^{-1}$ at the same composition and temperature. More recently Ussanowitsch, Sumarakowa, and Udowenko (*Acta Phys. Chim. U.R.S.S.*, 1939, **11**, 505) reported values of 0·0106 ohm^{-1} $cm.^{-1}$ at 25° and 0·0058 ohm^{-1} $cm.^{-1}$ at 10° for the conductivity of pure sulphuric acid. Reinhardt (*J. Amer. Chem. Soc.*, 1950, **72**, 3359) investigated the conductivity of solutions of sulphur trioxide and gave a value of 0·0108 ohm^{-1} $cm.^{-1}$ for the conductivity of the pure acid. In a very recent paper (*ibid.*, 1952, **74**, 804) Kunzler and Giauque have shown that the minimum conductivity at 10·37° occurs at 99·996 $\pm$ 0·001 wt. % sulphuric acid, but they did not give any specific conductivity values.

A detailed re-investigation of the electrical conductivity of the water–sulphur trioxide system at 25° in the neighbourhood of the composition of sulphuric acid is now reported. A few measurements have also been made at 10·4°.

Experimental

Conductivity Apparatus.—The Pyrex-glass cells used (Fig. 1) were a modified form of that originally designed by Shedlovsky (*J. Amer. Chem. Soc.*, 1932, **54**, 1411). The flask *A* was of about 500 $cm.^3$ capacity. The electrode chamber *C* was 1 cm. in diameter and 20 cm. long and contained at each end a platinum electrode *D*, approximately 0·5 cm. in diameter. The electrode chamber was designed to give a measured resistance of greater than 1000 ohms, to minimise the Parker effect, and to provide good thermal contact with the thermostat liquid. The function of the flask *A* and the three-way tap *E* was to facilitate the study of a series of different concentrations of solutions of the same solute. The electrodes were freshly platinised before each experiment. The cell constants were determined by using potassium chloride solutions of known concentration. Values of the specific conductivities of these solutions were interpolated from a curve based on Jones and Bradshaw's data (*J. Amer. Chem. Soc.*, 1933, **55**, 1780).

A small cell (Fig. 2) was also used in certain experiments in which the freezing points of the solutions were also measured. Its cell constant was determined in the manner described above.

* Part VIII, *J.*, 1950, 2997. The former serial title "Cryoscopic Measurements in Sulphuric Acid" has now been widened.

The bridge circuit was of conventional design and included a calibrated non-inductive dial resistance box, a non-inductive ratio-box, a balancing condenser across the resistance box and a simple Wagner earth. A.C. of 1000 cycles cm.$^{-1}$ was provided by a fixed-frequency Muirhead oscillator. The balance point was detected by means of a single-stage amplifier and head phones.

Materials.—Dilute oleum solutions were prepared by distilling sulphur trioxide from 60% oleum into 98% " AnalaR " sulphuric acid under reduced pressure at room temperature. " AnalaR " potassium chloride was recrystallised twice from conductivity water, and dried at 600° for 4 hours. Conductivity water was prepared freshly for each experiment in an all-glass

FIG. 1. *Conductivity cell.*

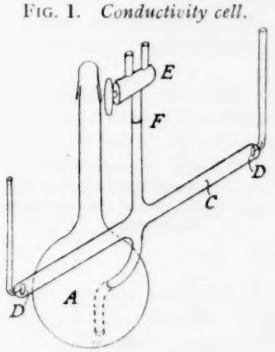
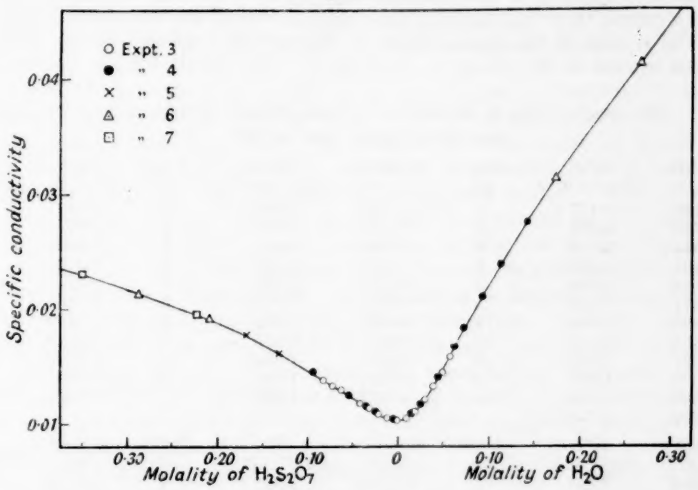


FIG. 2. *Conductivity cell for small amounts of solution.*

FIG. 3. *Specific conductivities of the system water–sulphur trioxide at compositions near that of sulphuric acid.*



(Pyrex) apparatus by distilling the laboratory distilled water from potassium permanganate and sodium hydroxide.

Method.—Measurements were made in an oil-filled thermostat kept at 25·00° ± 0·01°. A few measurements were made at 10·4°. The cell was weighed empty, the flask *A* was filled with a dilute oleum, and the cell weighed again. The electrode chamber was then filled by applying suction through the three-way tap *E*. This solution was allowed to run back into the flask, the flask well shaken, and another portion sucked up. The electrode chamber was always washed several times in this manner before being finally filled to a mark on the tube *F*. During the whole operation the solution in the cell was protected from atmospheric moisture by phosphoric oxide guard-tubes. The conductivity was measured after the cell had been in the thermostat for ¾ hour. The electrode chamber was then emptied, the flask shaken, the

electrode chamber refilled, and the conductivity measurement repeated in order to ensure that the solution had reached thermostat temperature and that the washing of the electrode chamber had been complete. Successive small weighed amounts of water were then added and the conductivity measured each time in the manner described above. The precise amount of sulphur trioxide in the initial acid was not known at the commencement of each experiment, but after all the conductivity measurements had been made all the concentrations could be calculated with the aid of the assumption that the composition at the minimum is that of sulphuric acid.

A number of experiments were also carried out in which the freezing point as well as the conductivity was measured for each composition. Freezing points were measured in the apparatus and by the method described in Part I (*loc. cit.*), and the conductivities were measured

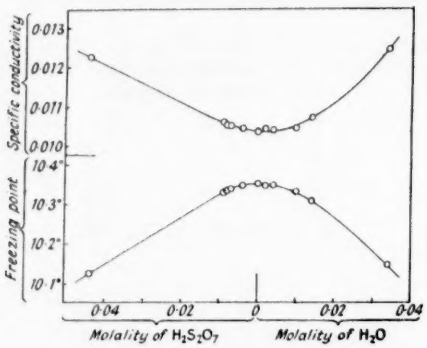


FIG. 4. *Comparison of specific conductivities and freezing points in the region of the freezing-point maximum.*

in the small cell shown in Fig. 2. Solutions were prepared in the cryoscope, the freezing point measured, and a sample then transferred to the conductivity cell and its conductivity measured.

Results.—The results of the measurement of the specific conductivity (κ) of the water–sulphur trioxide system at 25° are given in Table 1. The results for low concentrations of

TABLE 1. *The conductivity of the water–sulphur trioxide system at compositions near that of sulphuric acid at 25°.*

Expt. no.	Molality $H_2S_2O_7$	$10^2\kappa$, ohm^{-1} cm.$^{-1}$	Expt. no.	Molality $H_2S_2O_7$	$10^2\kappa$, ohm^{-1} cm.$^{-1}$	Expt. no.	Molality $H_2S_2O_7$	$10^2\kappa$, ohm^{-1} cm.$^{-1}$
7	1·5630	3·477	7	0·1043	1·493	3	0·0404	1·184
,,	1·1520	3·309	5	0·0935	1·454	4	0·0335	1·154
,,	0·9944	3·205	6	0·0803	1·387	6	0·0301	1·132
,,	0·8101	3·040	5	0·0752	1·370	4	0·0237	1·109
,,	0·6195	2·826	3	0·0710	1·335	5	0·0216	1·092
,,	0·4671	2·554	5	0·0661	1·315	6	0·0182	1·077
,,	0·3496	2·303	3	0·0617	1·286	4	0·0134	1·067
6	0·2863	2·127	5	0·0571	1·275	3	0·0110	1·047
7	0·2227	1·950	3	0·0509	1·234	6	0·0062	1·044
6	0·2075	1·903	4	0·0431	1·205	4	0·0032	1·041
5	0·1670	1·767	4	0·0401	1·205	—	0·0000	1·033
,,	0·1298	1·616						
Expt. no.	Molality H_2O	$10^2\kappa$, ohm^{-1} cm.$^{-1}$	Expt. no.	Molality H_2O	$10^2\kappa$, ohm^{-1} cm.$^{-1}$	Expt. no.	Molality H_2O	$10^2\kappa$ ohm^{-1} cm.$^{-1}$
6	0·7859	7·591	4	0·1149	2·385	4	0·0275	1·196
,,	0·6659	6·993	,,	0·0946	2·105	,,	0·0257	1·181
,,	0·5603	6·381	,,	0·0740	1·832	3	0·0197	1·114
,,	0·4541	5·676	,,	0·0635	1·673	4	0·0153	1·098
,,	0·3607	4·960	,,	0·0535	1·540	3	0·0100	1·053
,,	0·2675	4·133	,,	0·0445	1·409	4	0·0068	1·051
,,	0·1746	3·128	3	0·0392	1·326	6	0·0060	1·048
4	0·1442	2·758	3	0·0300	1·208	,,	0·0000	1·033

water and sulphur trioxide are also shown graphically in Fig. 3. On the aqueous side of the composition of sulphuric acid, concentrations are expressed as molalities of water, but on the sulphur trioxide side they are given, not as molalities of sulphur trioxide, but as molalities of disulphuric acid, the assumption having been made that the solute sulphur trioxide is converted almost completely in dilute solutions into disulphuric acid (cf. Part II, *J.*, 1950, 2493).

The results of the few measurements made at 10·4° are given in Table 2.

TABLE 2. *The conductivity of the water–sulphur trioxide system at compositions near that of sulphuric acid at* 10·4°.

Molality of $H_2S_2O_7$	$10^2\kappa$, ohm^{-1} cm.$^{-1}$	Molality of $H_2S_2O_7$	$10^2\kappa$, ohm^{-1} cm.$^{-1}$	Molality of H_2O	$10^2\kappa$, ohm^{-1} cm.$^{-1}$	Molality of H_2O	$10^2\kappa$, ohm^{-1} cm.$^{-1}$
0·0516	0·740	0·0072	0·587	0·0064	0·599	0·0678	1·139
0·0367	0·684	0·0000	0·580	0·0200	0·681	0·0990	1·447
0·0218	0·625			0·0363	0·826	0·1472	1·882

In order to determine the exact composition at which the conductivity minimum occurs, some experiments were carried out in which the freezing point as well as the conductivity at 25° was measured for each composition. The data obtained in these experiments are shown in Fig. 4.

It can be readily seen that, to within the accuracy of our measurements, the conductivity minimum at 25° occurs at the same composition as the freezing-point maximum, *i.e.*, at the composition of sulphuric acid. It certainly cannot differ from this composition by more than 0·003 mole kg.$^{-1}$. The value of the specific conductivity at the minimum in the conductivity curve, which is also therefore the conductivity of sulphuric acid, was found from the present results to be 0·01033 ohm^{-1} cm.$^{-1}$ at 25° and 0·00580 ohm^{-1} cm.$^{-1}$ at 10·4°.

DISCUSSION

Our value of the specific conductivity of sulphuric acid at 25° is compared with that of previous investigators in Table 3. Although our value is not as low as those of Hantzsch (*loc. cit.*) and Bergius (*loc. cit.*), it seems reasonable to suppose that our acid was pure, since

TABLE 3. *The specific conductivity of sulphuric acid at* 25° (κ in ohm^{-1} cm.$^{-1}$).

Hantzsch (1907)	0·0098	Ussanowitsch *et al.* (1939)	0·0106
Lichty (1908)	0·01041	Reinhardt (1950)	0·0108
Bergius (1910)	0·0097	This investigation (1952)	0·01033

it was prepared in the manner described in Part I and had a maximum freezing point of 10·36°, which was the highest freezing point we could obtain. Gable, Betz, and Maron recently (*J. Amer. Chem. Soc.*, 1950, **72**, 1445) obtained a value of 10·37°. That our specific conductivity value is probably reliable is emphasised by the fact that it was obtained numerous times in two independently calibrated cells.

Hantzsch's values (*loc. cit.*) cannot in any case be regarded as very reliable, for the conductivity cells they used were not particularly suitable for such a highly conducting liquid as sulphuric acid, and their measured resistances were consequently very small and hence not very accurate. Furthermore, the technique of making conductivity measurements has been considerably improved since Hantzsch's time. Lichty's value (*loc. cit.*) is in quite good agreement with ours, but the recent values of Ussanowitsch *et al.* (*loc. cit.*) and of Reinhardt (*loc. cit.*) are not. The reasons for these higher values are not clear, but Reinhardt's values of the conductivity of solutions of disulphuric acid are also in very poor agreement with ours and those of other workers, thus suggesting that his conductivity measurements are not reliable.

Sulphuric acid has a very large conductivity for a pure liquid, larger in fact than for any other liquid that has been investigated with the exception of nitric acid and fused salts. This may be attributed to its extensive self-dissociation, which has been shown by cryoscopic measurements (Parts I, II, and IV) to be partly an autoprotolysis $2H_2SO_4 = H_3SO_4^+ + HSO_4^-$ and partly a self-dehydration : $2H_2SO_4 = H_3O^+ + HS_2O_7^-$.

The disulphuric acid branch of the conductivity curve in Fig. 3 is less steep than the water branch, and this is in accord with the conclusion from cryoscopic measurements (Part II) that water is almost fully ionised according to the equation $H_2O + H_2SO_4 = H_3O^+ + HSO_4^-$, whereas sulphur trioxide is very largely converted into disulphuric acid, which is only partly ionised according to the equation $H_2S_2O_7 + H_2SO_4 = H_3SO_4^+ + HS_2O_7^-$. The conductivities of these two solutes are further discussed in relation to other solutes in Part XII (*J.*, 1953, 221).

In Fig. 5 a selection of the results given in Table 2 have been replotted, the concentrations of water and disulphuric acid being expressed in molarities by use of the density data reported in Part XI (*J.*, 1953, 215), and compared with the results of previous investigators. It may be seen that our results for water agree quite well with those of Lichty (*loc. cit.*) over the whole concentration range investigated, while the specific conductivities obtained by Hantzsch (*loc. cit.*) and by Bergius (*loc. cit.*) are as much as 10% lower than our values at corresponding concentrations. Our results for disulphuric acid do not agree very well with those of any of the previous investigators. The agreement with the results of Bergius (*loc. cit.*) is fair, his specific conductivity values being approximately 5% lower than ours.

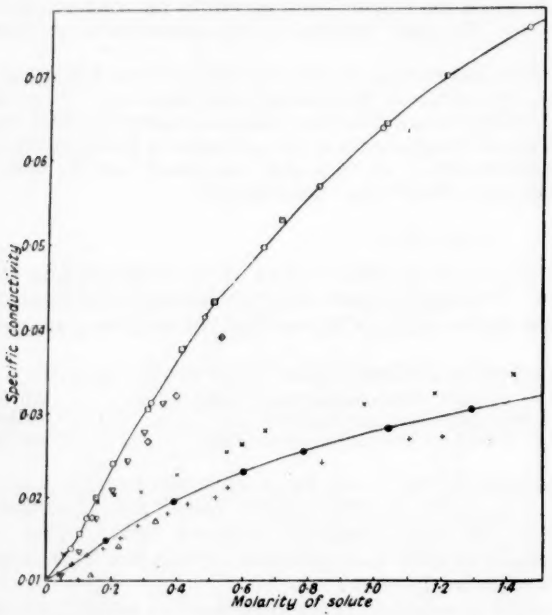


FIG. 5. *Comparison of the specific conductivities of water and disulphuric acid with the values obtained by earlier workers,*

H_2O: ○ *This investigation.* ⊡ *Lichty.* ▽ *Bergius.* ◇ *Hantzsch.*

$H_2S_2O_7$: ● *This investigation.* × *Reinhardt.* + *Bergius.* △ *Hantzsch.*

There is no agreement at all with Reinhardt's results (*loc. cit.*). Our results seem to be in agreement with those of Brand, Horning, and Thornley (*J.*, 1952, 1374) who, although they give no actual experimental results, state that the specific conductivities they obtained agreed best with those of Lichty (*loc. cit.*) for aqueous acids and those of Bergius (*loc. cit.*) for oleum.

We are grateful to the Egyptian Government for a scholarship awarded to one of us (S. W.)

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44. *Solutions in Sulphuric Acid. Part X.* Transport-number Measurements.*

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The apparent transport numbers of the lithium, sodium, potassium, silver, barium, and strontium ions in solutions of their hydrogen sulphates in sulphuric acid have been measured. The very small values obtained in every case have been interpreted as providing further evidence that the conductivity of these solutions is due very largely to the hydrogen sulphate ion which conducts almost entirely by a chain mechanism similar to that which had been proposed to explain the abnormal mobilities of the hydrogen and hydroxyl ions in water. The nature of the chain conduction process in sulphuric acid is discussed and compared with what is known concerning chain conduction in other solvents. The transport numbers of the cations investigated are compared and discussed, and their variation with concentration is also briefly discussed. Finally, the temperature variation of the transport number of the potassium ion is briefly discussed.

The earliest experiments on ionic transport in sulphuric acid were carried out by Hantzsch (*Ber.*, 1925, **58**, 941). He attempted to prove the presence of the nitracidium cation ($H_2NO_3^+$) in water–sulphuric acid–nitric acid mixtures by migration experiments. The electrode reactions at the cathode, however, resulted in considerable reduction of both acids which rendered the measurements very inaccurate, and Hantzsch was unable to detect any transport of nitric acid. Hammett and Lowenheim (*J. Amer. Chem. Soc.*, 1934, **56**, 2620) later demonstrated that there is a very small but real transport of barium and strontium ions in solution of their hydrogen sulphates. They measured the transport numbers of these ions and detected some variation with concentration. Angus and Leckie (*Trans. Faraday Soc.*, 1935, **31**, 958) electrolysed nitrosonium hydrogen sulphate in 18—19% oleum and showed that a migration of the nitrosonium ion occurred. Quite recently the difficulties encountered by Hantzsch in attempting to demonstrate the migration of nitric acid were overcome by Bennett, Brand, and Williams (*J.*, 1946, 975) by working in oleum solutions. They showed that in oleum containing 4—18% of sulphur trioxide the main subject of cathodic reduction was the oleum and found a definite transport of nitric acid towards the cathode. Other work has shown that this cationic form of nitric acid is the nitronium ion (see, *e.g.*, Gillespie and Millen, *Quart. Reviews*, 1948, **2**, 277). The reason that it is considerably easier to demonstrate the transport of cations in oleum than in sulphuric acid is that in oleum basic solutes, such as nitric acid, exist in the form of hydrogen disulphates rather than as hydrogen sulphates, and the hydrogen disulphate ion ($HS_2O_7^-$) has a very much smaller mobility than the hydrogen sulphate ion.

In the present work Hammett and Lowenheim's measurements on the transport numbers of the barium and strontium ions in solutions of their hydrogen sulphates have been repeated, and in addition, the transport numbers of the lithium, sodium, potassium, and silver ions in solutions of their hydrogen sulphates have been determined at 25°. The variation of the transport number of the potassium ion with temperature has also been investigated.

Experimental

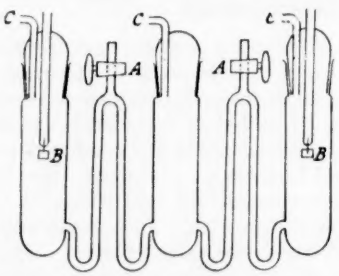
Apparatus.—All measurements were made by Hittorf's method in a cell similar to that used by Hammett and Lowenheim (*loc. cit.*). It contained three compartments (each about 50 c.c.), connected to each other by narrow bent tubes to minimise diffusion from one compartment to another (see Figure). Two taps, *A*, were joined to the connecting tubes so that the solutions in the three compartments could be readily separated by application of a small air-pressure. Platinum electrodes, *B*, were placed in each of the outer compartments. The outlet tubes, *C*, were protected with phosphoric oxide guard-tubes. The current used, 20—25 milliampères, was small enough to prevent any appreciable heating of the solution and consequent errors due to convection. The quantity of electricity was measured by a copper coulometer which had

* Part IX, preceding paper.

been checked against a silver coulometer constructed according to Rosa and Vinal's method (*Bur. Stand. Bull.*, 1936, **13**, 479). The cell was immersed in a thermostat at 25°. At the end of each experiment, the solutions in the three compartments were separated, removed, and weighed. After thorough mixing, samples were taken and analysed.

Methods of Analysis.—Barium and strontium were determined by diluting a weighed portion of the solution with a large excess of water in the case of barium and a 1 : 1 water–alcohol mixture in that of strontium, and filtering, washing, drying, and weighing in the usual manner. Silver determinations were carried out by diluting a weighed portion of the solution with a large excess of water, and precipitating silver chloride by slow addition of an excess of hydrochloric acid. The precipitate was then treated by standard procedures. Analysis for sodium, potassium, and lithium was carried out by slowly driving the sulphuric acid off a weighed portion of solution by prolonged heating in a platinum crucible. The resulting solid was then heated to constant weight at 600°.

Materials.—Sulphuric acid was prepared from a weak oleum by adding small quantities of water until a minimum conductivity of 0·0103 ohm^{-1} was obtained. The initial weak oleum was prepared by distilling sulphur trioxide from 60% oleum into 98% " AnalaR " sulphuric acid. Sodium, potassium, lithium, and silver sulphates were all " AnalaR " materials dried at



Transport-number apparatus.

150° and stored in a vacuum-desiccator. Barium sulphate was prepared by slow addition of a slight excess of sulphuric acid to a barium chloride solution. The precipitated barium sulphate was filtered off, washed, and ignited in a muffle furnace at 500°. Strontium sulphate was prepared similarly.

Results.—Table 1 contains the results of the measurements of the transport numbers of the

TABLE 1. *Apparent transport numbers.*

Solute	m	Q, coulombs	Equiv. gained by cathode compartment ($\times 10^4$)	Equiv. lost by anode compartment ($\times 10^4$)	t_c	t_a	t
$AgHSO_4$	0·2490	3329	9·62	8·46	0·028	0·024	0·026
	0·3056	4899	11·28	11·22	0·022	0·022	0·022
$KHSO_4$	0·6244	6166	19·18	19·42	0·030	0·030	0·030
	1·2262	6818	17·65	17·40	0·025	0·025	0·025
$NaHSO_4$	0·7918	7780	18·10	16·26	0·022	0·020	0·021
$LiHSO_4$	0·5562	5745	9·28	6·92	0·015	0·012	0·013
$Ba(HSO_4)_2$	0·1738	5175	4·94	4·80	0·009	0·009	0·009
	0·1969	5718	5·62	5·39	0·009	0·009	0·009
	0·2073	5632	5·38	3·94	0·009	0·007	0·008
	0·2292	9598	10·18	9·21	0·010	0·009	0·010
	0·2418	5644	4·41	4·39	0·008	0·007	0·008
	0·3062	7702	6·46	6·07	0·008	0·008	0·008
	0·5391	8314	4·21	3·87	0·005	0·005	0·005
	0·7981	9345	4·26	3·78	0·004	0·004	0·004
$Sr(HSO_4)_2$	0·2111	5764	4·55	4·11	0·008	0·007	0·007
	0·2788	7818	6·30	5·46	0·008	0·007	0·007
	0·5819	7620	4·06	3·34	0·005	0·004	0·005
	0·8247	9340	3·12	3·32	0·003	0·003	0·003

silver, potassium, lithium, sodium, barium, and strontium ions in solution of their hydrogen sulphates at 25° and at various concentrations.

The values given in this table are apparent or Hittorf transport numbers and no attempt has been made to determine true transport numbers by using a reference non-electrolyte as did Ham-

mett and Lowenheim (*loc. cit.*). It is exceedingly difficult to find a suitable reference non-electrolyte, for even trichloroacetic acid, used by Hammett and Lowenheim, is probably slightly ionised (see Part XII), and in any case there is considerable doubt as to the reliability of this method of determining true transport numbers since it is not possible to be certain that the reference substance does not preferentially " solvate " the electrolyte and thus get transferred with it (cf. Longsworth, *J. Amer. Chem. Soc.*, 1947, **69**, 1258).

The variation of the transport number of the potassium ion with temperature over the range 25—61° was also investigated, and the results (Table 2) show that there is probably a very slight increase in the transport number with increasing temperature.

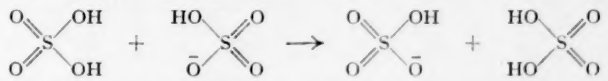
TABLE 2. *Apparent transport numbers of potassium hydrogen sulphate at different temperatures.*

Temp.	m	*Q*, coulombs	Equiv. gained by cathode compartment ($\times 10^4$)	Equiv. lost by anode compartment ($\times 10^4$)	t_c	t_a	t
25·0°	0·6244	7900	19·18	19·42	0·030	0·030	0·030
36·8	0·6536	7531	18·68	19·31	0·032	0·033	0·032
45·1	0·6388	8936	25·84	24·68	0·032	0·030	0·031
55·0	0·7098	7579	30·24	19·77	0·034	0·033	0·033
61·0	0·6556	7496	22·98	18·39	0·039	0·031	0·035

DISCUSSION

Abnormal Conduction in Sulphuric Acid.—The small differences between the transport numbers of different ions and the small variations with concentration being temporarily ignored, our results confirm those of Hammett and Lowenheim (*loc. cit.*) concerning the barium and strontium ions and show further that the transport numbers of the lithium, sodium, potassium, and silver ions in solutions of their hydrogen sulphates are also very small. As Hammett and Lowenheim (*loc. cit.*) pointed out, it is quite impossible to account for the extraordinarily small transport numbers of these cations by assuming that they are partly present in the form of negatively charged complex ions, as in the case of cadmium iodide in water, *e.g.*, $2KHSO_4 = K^+ + K(HSO_4)_2^-$. Such a hypothesis is contradicted by the cryoscopic evidence that all these substances ionise in a simple manner (Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1933, **55**, 1900; and Part I, *J.*, 1950, 2473), *e.g.*, $KHSO_4 = K^+ + HSO_4^-$. Moreover, the very small cation transport numbers cannot be attributed to there being other ionic species present in the solution resulting from the self-dissociation of the sulphuric acid. It is shown later that the relatively large conductivity of the pure solvent is almost entirely due to the ions resulting from the autoprotolysis, and this is almost completely repressed in the solutions we have investigated.

It appears therefore that the hydrogen sulphate ion has a mobility 50—100 times greater than that of the cations investigated. As was first suggested by Hammett and Lowenheim (*loc. cit.*), the only reasonable way to account for this abnormal mobility of the hydrogen sulphate ion is to assume that it conducts by a type of Grotthus chain mechanism, analogous to that generally accepted to explain the abnormal mobilities of the hydrogen and hydroxide ions in water. One step in this process which is repeated along a long chain of sulphuric acid molecules may be represented diagrammatically as follows:



Thus by a succession of proton transfers the charge of a hydrogen sulphate ion is transferred through the solution without the actual movement of any ion. It is often stated that, in order for the same molecules to take part in a similar process, they must rotate into new positions, and therefore the process of abnormal conduction consists of a combination of proton transfer and molecular rotation. This is a substantially correct but nevertheless misleading description of the process. Because of the very large excess of solvent molecules, any given solvent molecule will only occasionally take part in a conducting chain, and there will in general be ample time for it to rotate into its original position so that

molecular rotation could never be the rate-determining stage of chain conduction as it sometimes appears to be. Much more important is the fact that, because of the thermal motion of the molecules, any given molecule will, in general, not be in exactly the right position to receive a proton from, or pass a proton on to, a neighbouring molecule, and hence each molecule must undergo a certain amount of rotation when it takes part in a conducting chain. The fact that, having done so, it is left in a position in which it cannot repeat the process without rotating to a new position is largely irrelevant, since whether or not it has already taken part in a conducting chain a certain amount of rotation will be necessary.

By analogy with water, for which it is known that both the hydrogen and hydroxyl ions have abnormal mobilities, it might be expected that the hydrogen ion in sulphuric acid ($H_3SO_4^+$) would also have an abnormal mobility. That it does indeed have an abnormal mobility, which must be very nearly equal to that of the hydrogen sulphate ion, follows from the fact that the minimum in the specific conductivity–concentration curve for the system SO_3–H_2O occurs to within the limits of experimental error exactly at the composition H_2SO_4 (Part IX, *loc. cit.*). As a result of its self-ionisation, sulphuric acid contains small concentrations of hydrogen, hydrogen sulphate, hydroxonium, and hydrogen disulphate ions (Part IV, *J.*, 1950, 2516). The transport number of the hydroxonium ion has not been measured, but since it is known that at low concentrations water is at least 90% ionised (Part II, *J.*, 1950, 2493) and since it has been shown (Part IX, *loc. cit.*) that its conductivity is almost identical with that of potassium hydrogen sulphate, it follows that the hydroxonium ion must have a very small mobility like the potassium ion. The hydrogen disulphate ion has also been shown by conductivity measurements to have a very small mobility (forthcoming paper). Hence neither of these ions contributes very much to the conductivity of sulphuric acid, which must be due mainly to the hydrogen sulphate ion and probably also the hydrogen ion ($H_3SO_4^+$). If it is assumed that, like other ions except the hydrogen sulphate ion, the hydrogen ion has a very small mobility, then it may be seen that when sulphur trioxide is added to sulphuric acid, producing hydrogen ions and hydrogen disulphate ions, and the self-ionisation is correspondingly repressed, the conductivity would initially fall, as highly conducting hydrogen sulphate ions are replaced by poorly conducting hydrogen disulphate ions. Eventually, of course, because of the increasing concentration of ions in the solution, the conductivity would pass through a minimum, and then increase. The minimum would, however, occur on the sulphur trioxide side of the composition of sulphuric acid. On the other hand, if it is assumed that the hydrogen ion has a considerably larger mobility than even the hydrogen sulphate ion, a similar argument shows that the conductivity minimum would be on the aqueous side of the composition of sulphuric acid. In fact, the very small conductivity due to the hydroxonium and hydrogen disulphate ions being discounted, the minimum will occur at the composition H_2SO_4 only if the mobility of the hydrogen ion is equal to that of the hydrogen sulphate ion. The abnormal mobility of the hydrogen ion must be due to a similar mechanism, involving proton transfer and molecular rotation, to that which is responsible for the abnormal mobility of the hydrogen sulphate ion. A single step of this process may be represented diagrammatically in the following manner:

Whether the proton transfer or the molecular rotation is the rate-determining process in the abnormal conduction of the hydrogen and hydroxyl ions in water has been the subject of controversy (Eyring and Stearn, *J. Chem. Phys.*, 1937, **5**, 113; Wannier, *Ann. Physik*, 1935, **24**, 545), and there does not seem to be sufficient evidence to warrant a definite conclusion. Our conclusion that the mobilities of the hydrogen and hydrogen sulphate ions are equal or very nearly so provides some evidence, however, that in sulphuric acid molecular rotation is rate-determining. The first stage in the process of abnormal conduction is different for the two ions; for the hydrogen ion it is the transfer of a proton from a

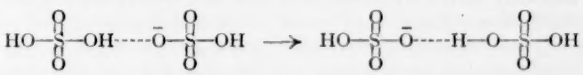
hydrogen to a sulphuric acid molecule, while for a hydrogen sulphate ion it is the transfer of a proton from a sulphuric acid molecule to a hydrogen sulphate ion, and it is unlikely that the rates of these two processes would be exactly the same. The second stage involving the rotation of sulphuric acid molecules is, however, common to both and must occur at the same rate in both cases. That molecular rotation should be the rate-determining step of abnormal conduction in sulphuric acid, even if it is not in water, can be very plausibly attributed to the high viscosity of sulphuric acid.

Comparison of Abnormal Conductivities in Different Solvents.—It is of interest to compare the abnormal mobilities of the hydrogen and hydrogen sulphate ions in sulphuric acid with the mobilities of analogous ions in other solvents. At first sight the mobilities of the hydrogen and hydrogen sulphate ions in sulphuric acid appear to be exceptionally abnormal, being 50—100 times greater than the mobilities of other ions. This is due, however, primarily to the high viscosity of sulphuric acid, which causes the mobilities of ions that conduct by the ordinary diffusion mechanism to be exceptionally small and not to any special facility of the chain conduction mechanism in sulphuric acid (cf. Hammett and Lowenheim, *loc. cit.*; and Part XII, *loc. cit.*).

In water the hydrogen and hydroxyl ions have mobilities some 4—5 times that of other ions, the hydrogen ion having a greater mobility than the hydroxyl ion. In methyl and ethyl alcohols the hydrogen ions, $CH_3{\cdot}\overset{+}{O}H_2$ and $C_2H_5{\cdot}\overset{+}{O}H_2$ respectively, have small abnormal mobilities, while the methoxide and ethoxide ions have normal mobilities. In ammonia both the ammonium (hydrogen) ion and the amide ion have normal mobilities, and in acetic acid and formic acid both the acetate and the formate ion respectively have normal mobilities. No abnormal mobility has been detected in hydrogen fluoride or hydrogen cyanide (Glasstone, Laidler, and Eyring, "The Theory of Rate Processes," McGraw Hill, New York, 1941). In nitric acid the nitrate ion appears to have a normal mobility (unpublished experiments by D. J. Millen and W. H. Lee).

It has been suggested (Glasstone, Laidler, and Eyring, *op. cit.*) that abnormal mobilities are related to the autoprotolysis constant of the solvent and only occur in solvents having a large value of this. As sulphuric acid has a very large autoprotolysis constant (Part IV, *loc. cit.*), the very abnormal mobilities of the hydrogen and hydrogen sulphate ions in this solvent would appear to provide support for this suggestion. It does not, however, account for the normal mobilities of the acetate and formate ions in acetic and formic acids respectively, both of which have larger autoprotolysis constants than water.

All those liquids in which abnormal mobilities due to chain conduction have been found are associated by hydrogen bonding, and it seems reasonable to suppose that in the proton-transfer stage of the process the proton moves along a hydrogen bond, *e.g.*,



and that the stronger the hydrogen bonding the easier the proton transfer becomes. It is noteworthy that the only solvents in which it is known that abnormal mobilities are considerably greater than the normal mobilities and in which the hydrogen ion and the corresponding anion *both* have abnormal mobilities are water and sulphuric acid. In water there is extensive association in three dimensions due to strong hydrogen bonds, and it seems very reasonable to assume that a similar extensive association occurs in sulphuric acid, whilst in all the other solvents that have been investigated, association is into linear polymers or dimers only, and in addition, in some cases, the hydrogen bonding is relatively weak and the degree of association therefore correspondingly small. This suggests that the nature and extent of the association in the liquid are of importance in determining the degree of abnormal mobility of the characteristic ions of the solvent. This is perhaps not an unreasonable conclusion, as it may be seen that the propagation of a conducting chain will be relatively easy in a liquid associated into large three-dimensional polymers since the majority of the molecules along the path of the chain, the average direction of which is, of course, determined by the applied field, will be in the correct position, or almost the correct position to continue the chain. Thus the average time of rotation of the molecules

in the chain will be relatively small, and if rotation is the rate-determining stage, the mobility will be correspondingly great. The mobility will obviously depend on the degree of association, as the smaller is the degree of association, the more molecules will have a random orientation rather than one fixed by the structure of the liquid, and so the longer will be the average time required for a molecule to rotate into a suitable position to carry on the chain, and hence the smaller will be the mobility. In a liquid associated into linear polymers, however, a chain will only be able to travel easily along such a polymer and since these will have a random orientation it will not in general be able to travel easily in the direction of the applied field. Either it will have to take a very circuitous path or it will have continually to jump from one group of associated molecules to another, each jump requiring a considerable amount of molecular rotation. In either case the mobility will obviously be much reduced. In a liquid associated into dimers, as acetic acid probably is, a considerable molecular rotation will be needed, at least every other time a proton is transferred, and the average time of rotation will be relatively large and the mobility correspondingly small.

Hence we may conclude that, where hydrogen bonding is strong, proton transfer fast, and molecular rotation is the rate-determining stage of chain conduction, the chain-conduction mobility will depend on the nature and extent of the association due to hydrogen bonds in the liquid. On the other hand, where the hydrogen bonding is relatively weak, proton transfer may be slower than molecular rotation and the extent and nature of the association will not then be of importance. In such a case, moreover, the whole process may be so slow that abnormal conduction is not observed.

Comparison of the Transport Numbers of Various Cations in Solutions of their Hydrogen Sulphates.—The results for the barium ion given in Table 1 are in fair agreement with those of Hammett and Lowenheim over the concentration range investigated, and our results for strontium are in good agreement with their single determination. A detailed comparison of the transport numbers of different cations is not possible at present as they have not all been investigated sufficiently thoroughly over a wide enough concentration range. The results given in Table 1 for the barium, strontium, and potassium ions show that there is a small but fairly definite decrease in the transport number with increasing concentration over the range 0·2—1·6 molal, and a similar decrease was found by Hammett and Lowenheim (*loc. cit.*) for the barium ion over approximately the same concentration range. We have not investigated the low concentration range in which Hammett and Lowenheim found an increase in the transport number of the barium ion with increasing concentration. This may, however, be quite real, and can be attributed to the presence in the solution at these low concentrations of the hydrogen ion from the autoprotolysis of the solvent, which, having as large a mobility as the hydrogen sulphate ion, would carry quite a large fraction of the current towards the cathode and hence cause a decrease in the transport number of the barium ion. It seems probable that there is a fairly general decrease in the transport numbers of alkali and alkaline-earth metal cations over the concentration range we have investigated. This can be attributed partly at least to the increasing viscosity of solutions of these cations with increasing concentration (Part XI, *J.*, 1953, 215) which reduces the normal mobility of the cations more than it does the abnormal mobility of the hydrogen sulphate ion (Part XII, *loc. cit.*).

Because of the variation of transport number with concentration, an exact comparison of the transport numbers of the cations we have investigated is not possible from the results given in Table 1. However, it seems very probable from these results that at a given concentration the transport numbers would decrease in the order

$$K^+ > Ag^+ > Na^+ > Li^+ > Ba^{++} > Sr^{++}$$

For the univalent cations this is the same order as is found in dilute solutions of various of their salts in water. It is generally accepted that in aqueous solutions this variation is due to an increase in solvation with increasing charge density on passing from the potassium ion to the lithium ion. This suggests that there might be a similar increase in solvation in this series in sulphuric acid. Other evidence that the extent of solvation does increase in the series $K^+ < Ag^+ < Na^+ < Li^+ < Ba^{++} < Sr^{++}$ is presented in Part XI.

Temperature Variation of the Transport Numbers of the Potassium Ion.—In Table 2 are presented the results of the determination of the transport number of the potassium ion in solutions of its hydrogen sulphate at very similar concentrations and at five different temperatures over the range 25—61°. There appears to be a very slight increase in the transport number with increasing temperature but this is scarcely larger than the probable experimental error. This suggests that, although the normal mobility of the cation increases with increasing temperature because of the decreasing viscosity of the solution, this must be almost exactly compensated by an increase in the abnormal mobility of the hydrogen sulphate ion because the rate of molecular rotation increases with increasing temperature.

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45. *Solutions in Sulphuric Acid. Part XI.* The Densities and Viscosities of Some Sulphuric Acid Solutions.*

By R. J. Gillespie and S. Wasif.

The densities and viscosities of dilute solutions in sulphuric acid of water, sulphur trioxide, some alkali and alkaline-earth metal hydrogen sulphates, nitric acid, sulphuryl chloride, and a number of organic compounds have been measured at 25°. Apparent molal volumes of some of the cations have been calculated and they are discussed in terms of their solvation. The viscosities of some of the solutions are also briefly discussed.

The measurement of the densities and viscosities of dilute solutions of a variety of solutes was originally undertaken to provide data necessary for the interpretation of the conductivity results presented in Part XII (*J.*, 1953, 221). The results obtained seemed, however, to be of sufficient interest to merit some independent discussion and they are accordingly presented here.

The only previous work on densities and viscosities of sulphuric acid solution has been concerned with the solutes water and sulphur trioxide, on which there is an extensive literature. No measurements of the densities or viscosities of solutions of other solutes appear to have been made.

Experimental

Sulphuric acid of minimum conductivity was prepared in a conductivity cell. A suitable quantity of the solute under investigation was added, the conductivity of the solution measured, and the concentration of the solute interpolated from a specific conductivity–concentration curve (Part XII, *loc. cit.*). Samples of the solution were transferred from the conductivity cell to the viscometer and pycnometer, the solution being protected throughout from contamination by atmospheric moisture. Further portions of the solute were then added, and the above procedure repeated. This method of determining the concentration of solutions from specific conductivity–concentration curves was easier and more rapid than making up each solution separately by weight, although the latter method was used in a few cases.

Densities were measured in a Sprengel-type pycnometer, and viscosities in simple Ostwald-type viscometers. The latter were calibrated by using suitable sucrose solutions of known viscosity (Bingham and Jackson, *Bur. Stand. Bull.*, 1917—18, **14**, 58).

Materials.—The preparation and purification of all the materials used is described in Parts X and XII (*locc. cit.*).

Results.—The density of sulphuric acid was found to be 1·8269 at 25° and its viscosity 24·54 centipoises at the same temperature. Table 1 contains the results of the measurements of the densities and viscosities of all the solutions investigated at 25°. These results are shown graphically in Figs. 1—7. Concentrations are expressed in molalities (m), *i.e.*, moles per 1000 g. of sulphuric acid. Viscosities are given in centipoises.

* Part X, preceding paper.

TABLE 1. *Densities and viscosities of solutions in sulphuric acid.*

m	d_4^{25}	$\eta^{25°}$
Solute: water.		
0·0330	1·8271	24·47
0·0660	1·8273	24·07
0·1200	1·8280	23·90
0·1840	1·8281	23·63
0·2610	1·8287	23·22
0·3440	1·8295	22·94
0·4500	1·8313	22·40
0·6106	1·8332	21·65
Solute: disulphuric acid, $H_2S_2O_7$.		
0·0190	1·8270	24·54
0·0470	1·8280	24·54
0·2250	1·8330	24·57
0·3550	1·8360	24·66
0·5360	1·8407	24·74
0·6920	1·8439	24·78
0·8350	1·8480	24·82
Solute: NH_4HSO_4.		
0·0964	1·8306	24·62
0·3741	1·8323	23·92
0·6556	1·8348	23·93
0·9245	1·8391	24·42
1·3000	1·8437	24·86
Solute: $KHSO_4$.		
0·2526	1·8446	25·23
0·4633	1·8578	26·14
0·5291	1·8622	26·89
0·8084	1·8780	28·30
1·199	1·8993	31·93
1·776	1·9276	38·84

m	d_4^{25}	$\eta^{25°}$
Solute: $NaHSO_4$.		
0·2755	1·8437	27·49
0·4392	1·8531	29·45
0·6968	1·8665	33 70
0·9108	1·8784	35·91
1·365	1·8994	44·19
1·454	1·9064	46·13
Solute: $LiHSO_4$.		
0·2491	1·8310	28·07
0·5712	1·8455	32·74
0·6331	1·8484	33·78
1·127	1·8660	42·82
Solute: $Ba(HSO_4)_2$.		
0·0650	1·8475	28·44
0·1122	1·8612	31·34
0·1997	1·8871	37·50
0·3917	1·9382	54·56
0·4486	1·9530	60·70
0·7901	2·0361	114·90
Solute: $Sr(HSO_4)_2$.		
0·0616	1·8416	28·19
0·2266	1·8767	39·81
0·3250	1·8980	48·70
0·5366	1·9382	73·87
0·7568	1·9775	114·7
0·8404	1·9920	137·7
Solute: NH_2Pr.		
0·0130	1·8255	24·46
0·0430	1·8224	24·32
0·0850	1·8168	23·96
0·1350	1·8107	23·72
0·2030	1·8033	23·28
0·3500	1·7850	22·80

m	d_4^{25}	$\eta^{25°}$
Solute: NH_2Ph.		
0·0199	1·8242	24·60
0·0799	1·8197	24·80
0·1444	1·8140	25·00
0·2100	1·8081	25·23
0·3570	1·7916	25·70
0·4140	1·7875	25·90
Solute: o-$C_6H_4(NH_2)_2$.		
0·0550	1·8269	26·43
0·1035	1·8270	27·85
0·1500	1·8273	29·52
0·1958	1·8285	31·55
0·2400	1·8295	33·30
0·3124	1·8306	36·56
0·3925	1·8308	41·00
Solute: AcOH.		
0·0470	1·8253	24·43
0·0830	1·8235	24·31
0·1100	1·8224	24·03
0·2430	1·8175	23·86
0·3570	1·8136	23·76
0·4275	1·8105	23·63
0·5740	1·8050	23·22
Solute: $Ph{\cdot}CO_2H$.		
0·0450	1·8235	24·73
0·0855	1·8190	25·13
0·1430	1·8120	25·31
0·2080	1·8071	25·69
0·2985	1·7996	26·13
0·3720	1·7920	26·64
0·4651	1·7832	27·25

m	d_4^{25}	$\eta^{25°}$
Solute: $COMe_2$.		
0·0450	1·8235	24·12
0·1350	1·8176	23·13
0·1885	1·8129	22·62
0·2320	1·8097	22·19
0·2950	1·8035	21·70
0·3750	1·7995	21·19
Solute: p-$C_6H_4Me{\cdot}NO_2$.		
0·0325	1·8233	24·57
0·0720	1·8168	24·60
0·1300	1·8080	24·62
0·1980	1·8000	24·67
0·2900	1·7864	24·72
0·3850	1·7710	24·80
Solute: $CPh_3{\cdot}OH$.		
0·1190	1·8109	25·05
0·2050	1·7981	25·48
0·3420	1·7804	25·98
0·5380	1·7593	26·93
Solute: HNO_3.		
0·0388	1·8305	24·05
0·0680	1·8330	23·80
0·0975	1·8350	23·52
0·1480	1·8400	23·02
0·2000	1·8430	22·48
0·2390	1·8492	22·02
0·3625	1·8600	20·80
Solute: SO_2Cl_2.		
0·0490	1·8260	24·13
0·0850	1·8256	23·92
0·1600	1·8240	23·49
0·2350	1·8231	22·97
0·3150	1·8217	22·55
0·4012	1·8209	22·01

DISCUSSION

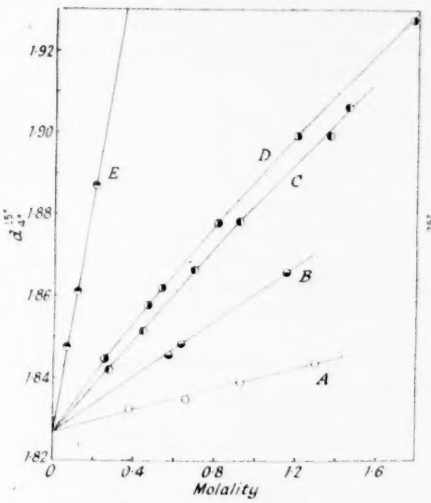
Although a large number of measurements have previously been made of the densities and viscosities of solutions of both water and sulphur trioxide in sulphuric acid (I.C.T., Vol. III, p. **57**; Vol. V, p. **13**; Landolt–Börnstein's "Physikalische-Chemische Tabellen," 1st edn., Vol. I, p. **397**; 2nd edn., Vol. I, p. **135**), relatively few values for the composition 100% H_2SO_4 have been recorded, and only one or two of these refer to 25°. Domke and Bein (*Z. physikal. Chem.*, **1905**, **43**, 125) found the density of 100% H_2SO_4 to be **1·8270** at 25°, with which our value of **1·8269** is in good agreement. Bergius (*ibid.*, **1910**, **72**, 357) found the viscosity of sulphuric acid to be **19·15** centipoises at 25°, and Dunstan (*J.*, 1908, **93**, 2179; *Proc.*, **1914**, **30**, 104) obtained a value of **23·5** centipoises at the same temperature, both of which are lower than our value of **24·54**. The value obtained by Bergius is certainly incorrect, and Dunstan's is probably somewhat in error, as it is very likely that his acid did not have exactly the composition 100% H_2SO_4, owing to the difficulty of adjusting the composition exactly to this value by ordinary chemical analysis.

With the exception of disulphuric acid and sulphuryl chloride, all the solutes we are considering ionise as hydrogen sulphates. Thus the effects of all these solutes on the viscosity and density are a measure of the relative effects of their cations. The separate effect of the hydrogen sulphate ion on these properties is of course not known, but for convenience we will assume it to be negligibly small and treat all the changes observed as being due to the cations. There is some justification for this assumption in that the hydrogen sulphate ion would be expected to fit easily into the structure of the acid without causing much disturbance and, since the effect of solute on the density and viscosity is

largely due to the changes that they cause in the structure of the solvent, it is reasonable to assume that the effect of the hydrogen sulphate will be rather small.

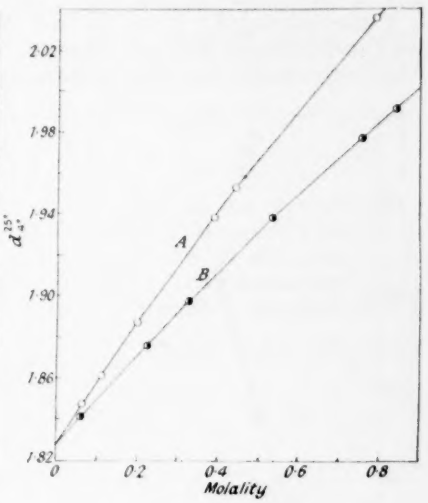
Densities and Apparent Molal Volumes.—It is clear from Figs. 1—4 that inorganic cations generally cause an increase in the density, this increase being roughly proportional

FIG. 1. *Densities of solutions at 25°.*



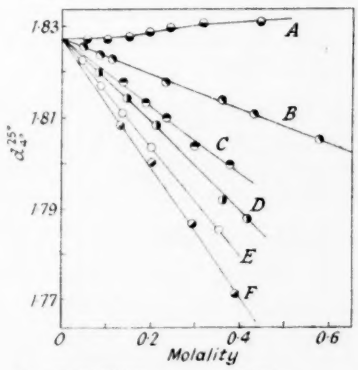
A, NH_4HSO_4. *D*, $KHSO_4$.
B, $LiHSO_4$. *E*, $Ba(HSO_4)_2$.
C, $NaHSO_4$.

FIG. 2. *Densities of solutions at 25°.*



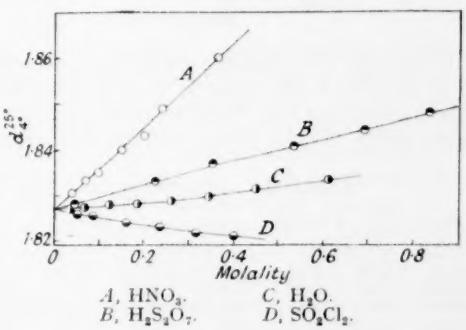
A, $Ba(HSO_4)_2$
B, $Sr(HSO_4)_2$.

FIG. 3. *Densities of solutions at 25°.*



A, o-$C_6H_4(NH)_2$. *D*, NH_2Ph.
B, AcOH. *E*, NH_2Pr^n.
C, $COMe_2$. *F*, p-$C_6H_4Me{\cdot}NO_2$.

FIG. 4. *Densities of solutions at 25°.*



A, HNO_3. *C*, H_2O.
B, $H_2S_2O_7$. *D*, SO_2Cl_2.

to the conentration, while organic cations generally cause a decrease, this again being roughly proportional to the concentration over the range investigated. It may also be seen that bivalent ions cause a larger increase in the density than univalent ions, and this is to some extent confirmed by the data given in Fig. 3, where it may be seen that the bivalent *o*-phenylenediamine cation is the only organic cation to cause an increase in the density. The density changes can be more conveniently and exactly discussed in terms of the apparent molal volumes of the solutes rather than in terms of the densities them-

selves. The apparent molal volume ϕ is related to the density of the solution ρ by the equation

$$\phi = \frac{1000}{m}\left\{\frac{1}{\rho} - \frac{1}{\rho_1}\right\} + \frac{M_2}{\rho}$$

where M_2 is the molecular weight of the solute, ρ_1 the density of the solvent, and m the molality of the solute. By use of this equation, the apparent molal volumes given in Table 2 were calculated. It can be seen that there is no very marked change of the apparent molal volume with concentration, although in some cases there seems to be a small but fairly regular increase with increasing concentration.

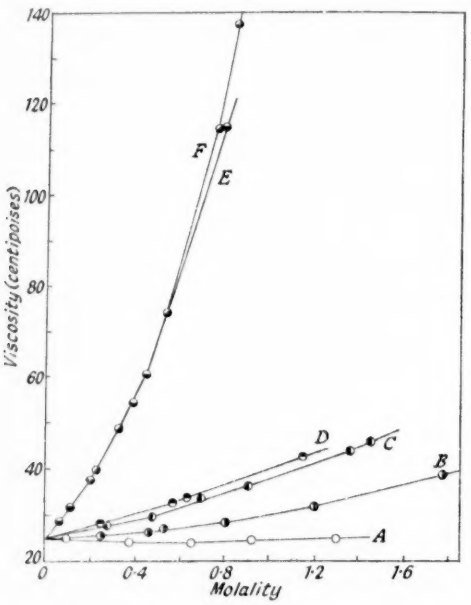


FIG. 5. *Viscosities of solutions at 25°.*

A, NH_4HSO_4. *D*, $LiHSO_4$.
B, $KHSO_4$. *E*, $Ba(HSO_4)_2$.
C, $NaHSO_4$. *F*, $Sr(HSO_4)_2$.

If we make the assumption that the apparent volume occupied by a hydrogen sulphate ion in solution is the same as that of a sulphuric acid molecule, which, in view of our earlier assumption that it causes little disturbance to the structure of sulphuric acid, is not unreasonable, we can easily calculate the apparent molal volumes of the cations in the

TABLE 2. *Apparent molal volume of some hydrogen sulphates.*

m	d_4^{25}	ϕ (cm.^{3})
Solute : NH_4HSO_4.		
0·3741	1·8323	58·5
0·6556	1·8348	59·1
0·9245	1·8391	58·6
1·3000	1·8347	58·6
Solute : $NaHSO_4$.		
0·2755	1·8437	46·6
0·4392	1·8531	46·6
0·9110	1·8784	47·4
1·364	1·8998	47·8
1·453	1·9064	47·4

m	d_4^{25}	ϕ (cm.^{3})
Solute : $KHSO_4$.		
0·2526	1·8446	52·9
0·4633	1·8578	53·8
0·5291	1·8622	53·6
0·8084	1·8780	54·1
1·199	1·8993	54·3
1·776	1·9276	54·5
Solute : $LiHSO_4$.		
0·5712	1·8455	46·8
0·6331	1·8484	46·3
1·127	1·8660	45·8

m	d_4^{25}	ϕ (cm.^{3})
Solute : HNO_3, *i.e.*, $(NO_2)(H_3O)(HSO_4)_2$.		
0·0690	1·8330	115
0·0994	1·8350	117
0·1525	1·8400	115
0·2082	1·8430	118
0·2508	1·8492	114
0·3903	1·8600	114

m	d_4^{25}	ϕ (cm.^{3})
Solute : *o*-$C_6H_4(NH_3)_2(HSO_4)_2$.		
0·2035	1·8285	164
0·2519	1·8295	163
0·3329	1·8306	163
0·4252	1·8308	163
Solute : $Ph{\cdot}NH_3{,}HSO_4$.		
0·2144	1·8081	132
0·3516	1·7916	137
0·4326	1·7875	135

solutions we have investigated. The values given in col. 3 of Table 3 were calculated by using a value of 54 c.c., the molal volume of sulphuric acid, for the apparent molal volume of the hydrogen sulphate ion. We see that very small or negative values for the apparent

molal volumes are obtained. In other words, the cations produce in most cases a decrease and not an increase in volume when in solution in sulphuric acid. This can be attributed to their effect on the solvent, which we describe as solvation, the sulphuric acid molecules that are bound strongly to the cations occupying less volume than the free solvent molecules.

TABLE 3. *Apparent molar volumes and solvation numbers of alkali and alkaline-earth cations.*

Solute	Mean ϕ (cm.^{3})	Mean ϕ_+ (cm.^{3})	r_+ (Å)	V_+ (cm.^{3})	Contraction volume, $(V_+ - \phi_+)$(cm.^{3})	Solvation number
NH_4HSO_4	59	5	1·48	8·2	3	(1)
$KHSO_4$	54	0	1·33	5·9	6	2
$NaHSO_4$	47	− 7	0·95	2·2	9	3
$LiHSO_4$	46	− 8	0·60	0·5	9	3
$Ba(HSO_4)_2$	89	−19	1·35	6·1	25	8
$Sr(HSO_4)_2$	86	−22	1·13	3·6	25	8

If we know the true volume of a cation we can calculate the contraction that it produces in the solvent by subtracting this true volume from its apparent molal volume. For the alkali and alkaline-earth metal ions we may assume that an approximate value of their true volumes may be obtained from their crystal radii. The volumes obtained in this way are given in col. 5 of Table 3, and the " contraction volumes " calculated from them

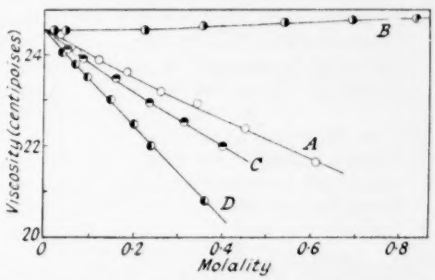


FIG. 6. *Viscosities of solutions at 25°.*

A, H_2O. *C*, SO_2Cl_2.
B, $H_2S_2O_7$. *D*, HNO_3.

in col. 6. Assuming that the larger the contraction produced by the ion the more strongly is it solvated, we see that the extent of solvation increases in the series

$$NH_4^+ < K^+ < Na^+ < Li^+ < Ba^{++} < Sr^{++}$$

With the exception of the ammonium ion, whose transport number was not measured, this is the same order as is suggested by the transport numbers of these ions (Part X, *loc. cit.*) and as has been found from the extent of solvation of these ions in aqueous solutions. It seemed worth while to attempt to express the degree of solvation of these cations in terms of solvation numbers in order that a more exact comparison might be made with other methods of estimating the extent of solvation. If we assume a value of unity for the solvation number of the ammonium ion as is obtained from cryoscopy (Part I, *loc. cit.*) we may then assume that the 3 c.c. volume contraction produced by the ammonium ion corresponds to one unit of solvation; thence the potassium ion, which produces a contraction of 6 c.c., has a solvation number of 2. The values listed in col. 7 of Table 3 were all calculated in this manner. The value found for the potassium ion agrees with that obtained by cryoscopy.

The apparent molal volumes of some of the other solutes investigated are given in Table 4. Mean apparent molal volumes of their cations have been calculated in the same way as before on the assumption that the molal volume of the hydrogen sulphate ion is 54 c.c. In order to interpret these values in terms of solvation, it is necessary to make some assumption about the true volumes of the cations, and this is more difficult to do than for the alkali and alkaline-earth metal ions. The volume of the hydroxonium ion will probably not differ greatly from that of the ammonium ion, which is given in Table 3 as 8·2 c.c. Hence from the apparent molal volume of the hydroxonium ion, given in Table 4 as 7 c.c., it follows that the hydroxonium ion causes a solvent contraction of ~1 c.c.,

corresponding to a solvation number of 0·4. A value of unity for this solvation number was obtained from cryoscopy (Part II, *loc. cit.*). Nitric acid is known from conductivity, cryoscopic, and other evidence (Gillespie and Millen, *Quart. Reviews*, 1948, **2**, 277) to ionise

TABLE 4. *Apparent molal volumes of water, nitric acid, aniline, and o-phenylenediamine.*

Solute	Mean ϕ (cm.^{3})	Mean ϕ_+ (cm.^{3})
Water, $(H_3O)(HSO_4)$	61	7
Nitric acid, $(NO_2)(H_3O)(HSO_4)_2$	115	7
Aniline, $Ph{\cdot}NH_3HSO_4$	135	81
o-Phenylenediamine, $[C_6H_4(NH_3)_2](HSO_4)_2$	163	57

according to the equation $HNO_3 + 2H_2SO_4 = NO_2^+ + H_3O^+ + 2HSO_4^-$. Hence, the apparent molal volume of the cations listed in Table 4 is actually the sum of the apparent molal volumes of the nitronium and hydroxonium ions. From the apparent molal volume of the hydroxonium ion also given in this table, it may be seen that the nitronium ion has a mean apparent molal volume of 0 c.c. It is difficult to make any reasonable assumption

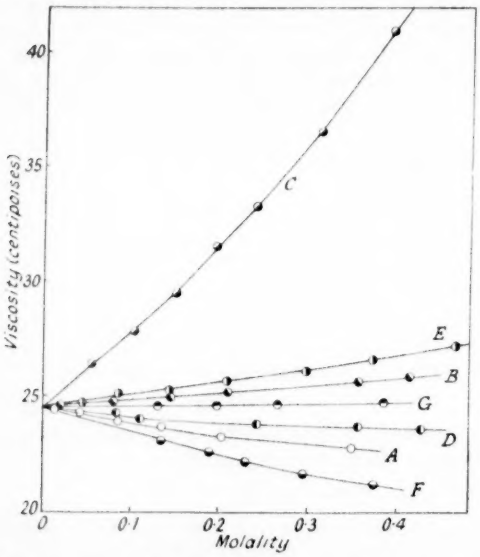


FIG. 7. *Viscosities of solutions at 25°.*

A, NH_2Pr^n. *E*, $Ph{\cdot}CO_2H$.
B, NH_2Ph. *F*, $COMe_2$.
C, $o\text{-}C_6H_4(NH_2)_2$. *G*, $p\text{-}C_6H_4Me{\cdot}NO_2$.
D, AcOH.

about the true molal volume of the nitronium ion and hence to calculate the solvation number, but its zero apparent molal volume leaves no doubt that it is solvated. Cryoscopic measurements (Part III) have given a value of 2 for the solvation number of the nitronium ion.

A comparison of aniline and *o*-phenylenediamine is of some interest. The true volumes of their cations would be expected to be rather similar, with the *o*-phenylenediamine having the slightly greater volume. The apparent molal volume of the *o*-phenylenediamine cation is, however, considerably less than that for the anilinium ion, which can be attributed to the greater solvation of the doubly charged *o*-phenylenediamine cation.

Viscosities of Solutions.—It may be seen from Fig. 5 that inorganic cations generally increase the viscosity of sulphuric acid, the effect of the bivalent ions being particularly great, although the ammonium ion gives a slight initial decrease followed by a slight increase with increasing concentration. The organic cations that we have investigated do not, as may be seen from Figs. 6 and 7, cause very large changes in the viscosity, with the exception of the cation of *o*-phenylenediamine, which gives a rather large increase comparable to that produced by the bivalent inorganic cations.

These viscosity changes may be explained in terms of the effects of the cations on the structure of the solvent. The small inorganic cations cause a "tightening" of the structure of the solvent around the ion, pulling the solvent molecules strongly together,

considerably restricting their freedom of movement, and thus increasing the viscosity. It is reasonable to expect, therefore, that their effect will be related to their degree of solvation and indeed it may be seen from Fig. 5 that the order of increasing viscosity of their solutions is the same as that of their degree of solvation as derived from density measurements, namely,

$$NH_4^+ < K^+ < Na^+ < Li^+ < Ba^{++} < Sr^{++}$$

In addition to the effect caused by their solvation, the large organic cations will tend to disrupt the structure of the surrounding solvent, as they will not fit easily into it, and this will probably be accompanied by a decrease in viscosity. A more detailed interpretation of the viscosities that we have determined does not seem possible at the present stage of our knowledge of these solutions.

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46. *Solutions in Sulphuric Acid. Part XII.* Electrical Conductivity Measurements.*

By R. J. GILLESPIE and S. WASIF.

The conductivities of solutions in sulphuric acid of ammonium, lithium, sodium, potassium, strontium, and barium hydrogen sulphate, and acetic acid, benzoic acid, acetone, *n*-propylamine, aniline, methyl and ethyl alcohols, nitric acid, triphenylmethanol, *o*-phenylenediamine, dinitrogen tetroxide, hexamethylenetetramine, *p*-nitrotoluene, dichloroacetic acid, sulphuryl chloride, and trichloroacetic acid have been measured.

The effects of the nature of the cation and of concentration on the conductivity of the hydrogen sulphate ion are discussed. The equivalent conductivity of this ion in sulphuric acid is compared with those of the hydrogen and hydroxide ions in water, and the conclusion is drawn that in sulphuric acid molecular rotation is the rate-determining stage of chain conduction, whereas in water proton-transfer is rate-determining.

On the basis of the results of the conductivity measurements, the solutes have been classified as strong, weak, or non-electrolytes, and the strong electrolytes have been further classified according to the number of hydrogen sulphate ions produced by one molecule of electrolyte. The use of conductivity measurements in determining the nature and extent of ionisation of a solute is discussed and compared with the corresponding use of cryoscopic measurements. The effect of non-electrolytes on the conductivity of sulphuric acid is discussed.

THERE has been very little previous work on conductivity measurements in sulphuric acid except that concerned with the solutes water and sulphur trioxide which has been discussed in Part IX (*J.*, 1953, 204). Hantzsch (**Z.** *physikal. Chem.*, 1907, **61**, 257) investigated the conductivities in sulphuric acid of a wide variety of solutes including the alkali-metal hydrogen sulphates, ammonium hydrogen sulphate, and water, which he showed had reasonably constant and similar equivalent conductivities, and he took the values of the equivalent conductivities of these solutes to be characteristic of a binary electrolyte. Although the equivalent conductivities of the alkali-metal hydrogen sulphates were all similar there were small but definite differences between them, which indicated that the equivalent conductivity increased with increasing molecular weight of the cation, which Hantzsch attributed to an increase in the mobility of the cation with increasing molecular weight. Certain organic compounds which he considered from the results of cryoscopic measurements to behave as binary electrolytes also gave equivalent conductivities similar to, although generally slightly smaller than, those of the alkali hydrogen sulphates. Hantzsch took this as confirmation of their behaviour as binary electrolytes. He concluded also that dichloroacetic acid behaves as a weak acid and that oxalic acid, trichloroacetic acid, trinitro-

* Part XI, preceding paper.

phenol, phthalic anhydride, and dimethyl sulphate behave as non-electrolytes. Bergius (*ibid.*, 1910, **72**, 338) later carried out very similar work, and attempted to investigate more dilute solutions than Hantzsch had done. He found somewhat different equivalent conductivity values and disputed Hantzsch's claim that the equivalent conductivity was independent of concentration. The general qualitative conclusions of both Hantzsch and Bergius were largely correct, the differences between their results arising mainly from their lack of understanding of the self-dissociation of the sulphuric acid and its repression by added electrolytes; thus they both always incorrectly subtracted the conductivity of the solvent from that of the solution before calculating the equivalent conductivity of the solute.

Usanovitch and his co-workers (*Physikal. Z. Sovietunion*, 1933, **4**, 134; *J. Gen. Chem. U.S.S.R.*, 1935, **5**, 701, 709; 1946, **16**, 1987) studied the conductivities and viscosities of a number of binary systems involving sulphuric acid and an organic compound, *e.g.*, nitrobenzene, trichloroacetic acid, and ether, and claimed that their results showed the existence of various addition compounds *e.g.*, $2M,H_2SO_4$, M,H_2SO_4, $M,2H_2SO_4$ (M = nitrobenzene). Recently Reinhardt (*J. Amer. Chem. Soc.*, 1950, **72**, 3359) has reported a few measurements on the conductivity of potassium hydrogen sulphate in dilute oleums: his results will be discussed in Part XIII.

In the present work the conductivities of solutions of a wide variety of solutes have been studied over a large concentration range. Many of these solutes have previously been investigated cryoscopically (cf. Parts I—VII and references contained therein), and their modes and degree of ionisation established.

Experimental

Apparatus and Experimental Procedure.—The conductivity apparatus has been described in Part IX (*loc. cit.*). Sulphuric acid was prepared in the conductivity cell by adding weighed amounts of water to a weighed amount of dilute oleum until the minimum conductivity was obtained. Successive weighed portions of the solute were then added, and the conductivity measured each time as described in Part IX.

Preparation and Purification of Materials.—The purification of ammonium sulphate and the alkali and alkaline-earth metal sulphates that were used was described in Part X (*J.*, 1953, 209). Methyl alcohol was dried and purified by fractionation through an efficient column. A middle fraction, b. p. 65·0°, was collected.

Ethyl alcohol. To the alcohol (1 l.) ethyl succinate (25 g.) and sodium (8 g.) were added, the mixture refluxed for 4 hours, the alcohol fractionated, and a fraction, b. p. 78·2°, collected (Smith, *J.*, 1927, 1288).

Triphenylmethanol was recrystallised several times from carbon tetrachloride; it had m. p. 162°. *n*-Propylamine was redistilled three times through an efficient column, and a fraction of b. p. 47·5° finally collected. Aniline, twice distilled from zinc dust, had b. p. 180°. *o*-Phenylenediamine was dissolved in hot water containing sodium dithionite (hydrosulphite) and charcoal, filtered, and allowed to crystallise. The colourless crystals obtained were washed with ice-cold water and dried in a vacuum-desiccator; m. p. 100—101°. Hexamethylenetetr-

Table 1. *Specific conductivities of some alkali and alkaline-earth metal hydrogen sulphates at 25°.*

M, mol. l.$^{-1}$	$10^3\kappa$	M, mol. l.$^{-1}$	$10^3\kappa$
Ammonium hydrogen sulphate.			
0·0268	1·085	0·3214	3·269
0·0417	1·150	0·6152	5·000
0·0600	1·300	1·0384	6·776
0·0825	1·450	1·2984	7·603
0·1066	1·680	1·4836	8·114
0·1199	1·758	1·6660	8·602
0·1381	1·960	1·9002	9·061
0·1773	2·300	1·9990	9·226
Sodium hydrogen sulphate.			
0·1318	1·736	1·4946	6·468
0·3206	2·997	1·8502	6·828
0·6972	4·711	2·2900	7·042
0·9666	5·505		
Potassium hydrogen sulphate.			
0·0568	1·256	0·1981	2·315
0·1251	1·740	0·2532	2·170
0·3602	3·380	1·0278	6·360
0·4934	4·156	1·1568	6·695
0·6242	4·783	1·3336	7·112
0·8686	5·834	1·4074	7·224
		1·6148	7·593
Lithium hydrogen sulphate.			
0·1342	1·760	1·0438	5·334
0·3794	3·277	1·2792	5·683
0·6112	4·247	1·5406	5·957
0·8248	4·876	1·7292	6·087
Strontium hydrogen sulphate.			
0·0842	1·923	0·5765	4·882
0·1705	2·851	0·6750	5·086
0·2853	3·824	0·8069	5·095
0·3844	4·360	0·9290	5·028
0·4666	4·650		
Barium hydrogen sulphate.			
0·0688	1·733	0·2599	3·658
0·1371	2·580	0·2988	3·941
0·3865	4·360	0·8448	5·247
0·4760	4·693	0·9513	5·260
0·6096	5·016	1·042	5·234
0·6640	5·152	1·122	5·193
0·7147	5·160	1·200	5·135

TABLE 2. *Specific conductivities of some strong electrolytes at 25°.*

M, mol. l.$^{-1}$	100κ	M, mol. l.$^{-1}$	100κ	M, mol. l.$^{-1}$	100κ	M, mol. l.$^{-1}$	100κ	M, mol. l.$^{-1}$	100κ	M, mol. l.$^{-1}$	100κ
Acetic acid.				n-*Propylamine.*				*Triphenylcarbinol.*			
0·1105	1·622	0·6174	4·700	0·1000	1·547	0·6850	5·140	0·0130	1·081	0·0425	1·353
0·2877	2·908	0·7760	5·328	0·2169	2·432	0·8206	5·724	0·0205	1·145	0·0873	2·128
0·4473	3·872	0·9548	5·908	0·3518	3·377	0·9554	6·162	0·0327	1·291		
Benzoic acid.				0·4338	3·933	1·0750	6·513				
0·1078	1·568	0·6731	4·535	0·5688	4·598			*o-Phenylenediamine.*			
0·2592	2·639	0·7770	4·825	*Aniline.*				0·0474	1·480	0·3413	4·890
0·3815	3·352	0·9310	5·140	0·0693	1·354	0·7103	5·076	0·0737	1·880	0·4452	5·408
0·5188	3·994			0·2365	2·640	0·8266	5·456	0·0954	2·230	0·5526	5·820
Acetone.				0·3437	3·356	0·9607	5·813	0·1000	2·371	0·6767	6·116
0·0220	1·064	0·4953	4·288	0·4680	4·055	1·0670	6·033	0·2037	3·690		
0·0781	1·351	0·6837	5·259	0·5851	4·599						
0·1128	1·748	0·7515	5·980	*Methyl alcohol.**				*Dinitrogen tetroxide.**			
0·1901	2·223	1·0480	6·500	0·0954	1·519	0·8069	5·562	0·0027	1·042	0·0379	1·619
0·3713	3·527			0·2564	2·735	0·9455	6·047	0·0072	1·070	0·0463	1·808
Nitric acid.				0·4374	3·869	1·104	6·533	0·0143	1·157	0·0598	2·111
0·0080	1·052	0·0850	2·065	0·6008	4·705	1·296	7·020	0·0210	1·265	0·0934	2·819
0·0148	1·091	0·1040	2·353	*Ethyl alcohol.**				0·0292	1·431	0·1216	3·379
0·0219	1·158	0·1115	2·450	0·0150	1·044	0·5175	4·380				
0·0292	1·237	0·2192	3·756	0·0394	1·124	0·7016	5·216	*Hexamethylenetetramine.**			
0·0402	1·381	0·3452	5·089	0·0817	1·408	0·8220	5·657	0·0089	1·146	0·0520	2·332
0·0524	1·563	0·5100	6·303	0·2138	2·467	1·001	6·222	0·0221	1·473	0·0743	2·902
0·0615	1·706	0·6525	7·105	0·3043	3·132			0·0325	1·758	0·0969	3·430

* The molarities of these solutes were calculated from the weight concentrations on the assumption that the densities of their solutions are the same as that of sulphuric acid.

TABLE 3. *Specific conductivities of some weak electrolytes at 25°.*

M, mol. l.$^{-1}$	100κ	M, mol. l.$^{-1}$	100κ	M, mol. l.$^{-1}$	100κ	M, mol. l.$^{-1}$	100κ	M, mol. l.$^{-1}$	100κ	M, mol. l.$^{-1}$	100κ
p-*Nitrotoluene.*				*Dichloroacetic acid.**				*Disulphuric acid.*†			
0·0911	1·304	0·5581	2·523	0·1109	1·166	0·4938	1·665	0·0248	1·056	0·7870	2·554
0·2421	1·841	0·6345	2·626	0·2421	1·355	0·6359	1·835	0·1870	1·493	1·039	2·826
0·3205	2·069	0·7558	2·742	0·3593	1·512	0·7865	1·964	0·3918	1·950	1·291	3·040
0·3984	2·247	0·9018	2·849					0·6011	2·303		
0·4816	2·406										

* See footnote to Table 2. † Taken from the results given in Table 1 of Part IX.

TABLE 4. *Specific conductivities of some non-electrolytes at 25°.*

M, mol. l.$^{-1}$ Solute	H_2SO_4	100κ	M, mol. l.$^{-1}$ Solute	H_2SO_4	100κ	M, mol. l.$^{-1}$ Solute	H_2SO_4	100κ	M, mol. l.$^{-1}$ Solute	H_2SO_4	100κ
Sulphuryl chloride.						*Trichloroacetic acid.**					
0·0000	18·62	1·033	0·4292	17·89	0·966	0·0000	18·62	1·033	0·3502	18·03	0·983
0·1212	18·42	1·016	0·5237	17·72	0·951	0·1272	18·41	1·016	0·4741	17·84	0·970
0·2005	18·28	1·002	0·6711	17·47	0·929	0·2451	18·22	0·999	0·5549	17·70	0·961
0·2853	18·10	0·989	0·7935	17·23	0·911						

* See footnote to Table 2.

amine was twice recrystallised from alcohol. Acetic acid was distilled from 100% sulphuric acid at room temperature. Benzoic acid was twice recrystallised from hot water and dried in a vacuum-desiccator; m. p. 121°. Dichloroacetic acid was distilled at 26 mm., and the fraction of b. p. 105—107° collected. Trichloroacetic acid was distilled, and the fraction of b. p. 194—196° collected.

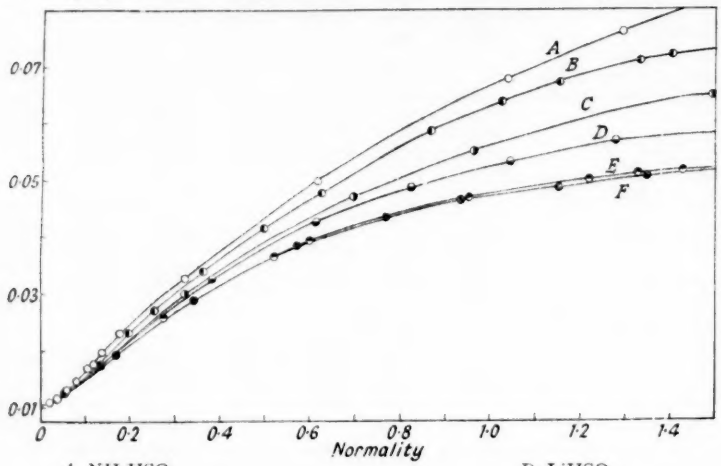
Acetone. "AnalaR" material was dried (K_2CO_3) and then distilled through an efficient column, the fraction of b. p. 56·5—57·0° being collected.

Nitric acid was prepared by the method described, *e.g.*, by Hughes, Ingold, and Reed (*J.*, 1950, 2400). Dinitrogen tetroxide was prepared by the method described in Part III (*J.*, 1950, 2504). Sulphuryl chloride was distilled several times, finally through an efficient column, the fraction of b. p. 69·1° being collected.

Results.—The specific conductivities, κ, at 25° of all the electrolytes investigated are listed in Tables 1—4, and a selection of them are plotted against concentration in Figs. 1—5. The

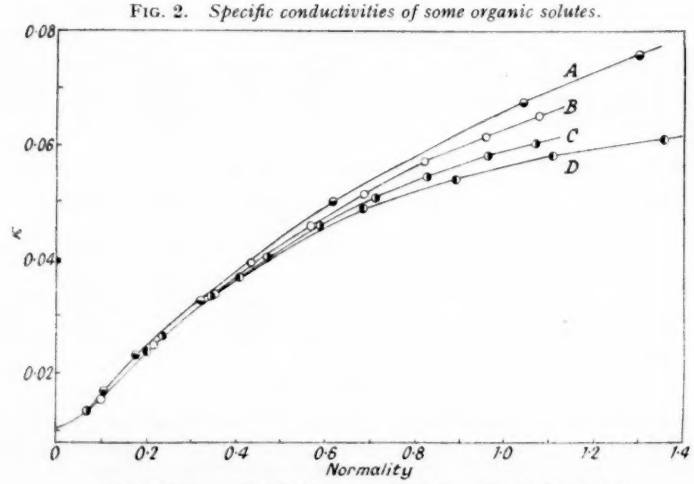
molarities, M, given in the tables have been calculated from the weight concentrations by utilising density values interpolated from curves based on the data recorded in Part XI. For a few solutes for which the density measurements were not made it was assumed that the densities of their solutions were the same as that of pure sulphuric acid.

FIG. 1. *Specific conductivities of some alkali and alkaline-earth metal hydrogen sulphates.*



A, NH_4HSO_4.
B, $KHSO_4$.
C, $NaHSO_4$.
D, $LiHSO_4$.
E, $Ba(HSO_4)_2$.
F, $Sr(HSO_4)_2$.

FIG. 2. *Specific conductivities of some organic solutes.*



A, NH_4HSO_4. *B*, $NH_2Pr^n_2$. *C*, NH_2Ph. *D*, o-$C_6H_4(NH_2)_2$.

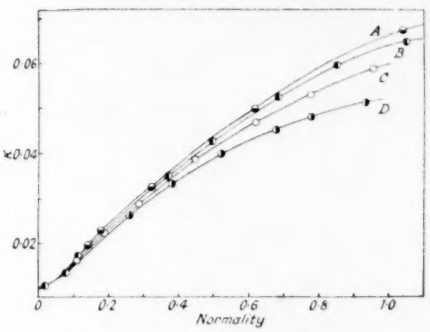
The equivalent and molar conductivities listed in Tables 5 and 6 were calculated from specific-conductivity values taken from plots of specific conductivity against concentration such as are shown in Figs. 1—3. Values of the equivalent and molar conductivity are not listed for solutions containing a total added hydrogen sulphate ion concentration of less than 0·1N since for smaller concentrations the repression of the autoprotolysis of the solvent is substantially incomplete and a correction should be made for this in calculating the equivalent or molar conductivity. For higher concentrations of added hydrogen sulphate ion the conductivity due to the autoprotolytic ions may be ignored without serious error (Part XIII, to follow).

DISCUSSION

The Conductivity of Some Alkali and Alkaline-earth Metal Hydrogen Sulphates, and the Mechanism of Conduction in Sulphuric Acid.—The conclusion drawn from transport-number measurements (Part X), *viz.*, that the conductivity of all basic solutes, *i.e.*, solutes that ionise as hydrogen sulphates, is due almost entirely to the chain conduction of the hydrogen sulphate ion, appears to suggest that all such solutes should have very similar conductivities. It is immediately apparent, however, from Fig. 1 and from the values of the equivalent conductivities listed in Table 5 that this is not so. The differences between the conductivities of these solutes are much too large to be attributed, as Hantzsch suggested, to the small differences between the mobilities of their cations, and it must therefore be concluded that the mobility of the hydrogen sulphate ion depends on the nature of the cation.

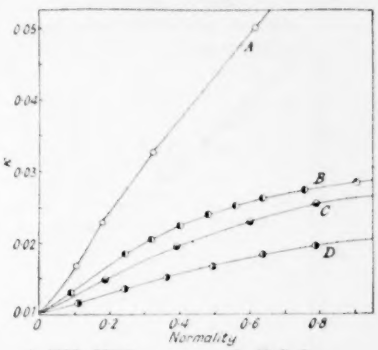
It may also be seen from the results in Table 5 that Hantzsch's conclusion that the equivalent conductivities of these solutes were constant and independent of concentration

FIG. 3. *Specific conductivities of some organic solutes.*



A, NH_4HSO_4. *C*, AcOH.
B, $COMe_2$. *D*, $Ph{\cdot}CO_2H$

FIG. 4. *Specific conductivities of some weak electrolytes.*



A, $NH_4{\cdot}HSO_4$. *C*, $H_2S_2O_7$.
B, $p\text{-}C_6H_4Me{\cdot}NO_2$. *D*, $CHCl_2{\cdot}CO_2H$.

is incorrect, for there is a steady and marked decrease in the equivalent conductivity with increasing concentration in each case. This is also apparent from the shape of the specific

TABLE 5. *Equivalent conductivities of some alkali and alkaline-earth metal hydrogen sulphates.*

	NH_4HSO_4		$KHSO_4$		$NaHSO_4$		$LiHSO_4$		$Ba(HSO_4)_2$		$Sr(HSO_4)_2$	
N	100κ	Λ	100κ	Λ	100κ	Λ	100κ	Λ	100κ	Λ	100κ	Λ
0·1	1·58	158	1·56	156	1·52	152	1·52	152	1·52	152	1·52	152
0·2	2·40	120	2·32	116	2·18	109	2·17	108	2·16	105	2·10	105
0·3	3·16	105	3·02	101	2·86	95·3	2·80	93·3	2·68	89·3	2·68	89·3
0·4	3·81	95·3	3·64	91·0	3·44	86·0	3·37	84·2	3·18	79·5	3·18	79·5
0·6	4·93	82·2	4·66	77·7	4·38	73·0	4·24	70·7	3·95	65·8	3·95	65·8
0·8	5·88	73·5	5·55	69·4	5·04	63·0	4·80	60·0	4·41	55·1	4·41	55·1
1·0	6·63	66·3	6·28	62·8	5·59	55·9	5·33	53·3	4·76	47·6	4·73	47·3
1·2	7·30	60·8	6·84	57·0	6·06	50·5	5·57	46·4	5·00	41·7	4·94	41·2
1·4	7·92	56·6	7·21	51·5	6·38	47·8	5·80	41·4	5·16	36·9	5·10	36·4

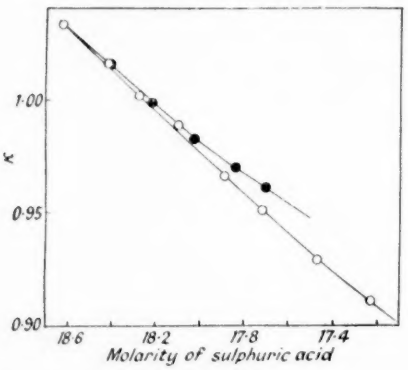
conductivity–concentration curves in Fig. 1. In each case there is an initial curvature convex to the concentration axis due to the repression of the self-ionisation by the added solute followed by a curvature in the opposite direction. The fact that in the latter region the specific conductivity does not increase linearly with concentration but rather more slowly indicates that the equivalent conductivity of the electrolyte is decreasing, *i.e.*, the mobility of the hydrogen sulphate ion decreases with increasing concentration.* Thus

* We shall assume that all the solutes we are at present considering behave as completely strong electrolytes. This seems reasonable in view of the very probable high dielectric constant of sulphuric acid (cf. Part I) which would make incomplete ionisation or ion-pair formation very unlikely.

we may conclude that the mobility of the hydrogen sulphate ion depends on its concentration and also on the nature of the cation. The similar dependence of the mobility of an ion in aqueous solution on its concentration and the nature of the other ions present is attributed on the Debye–Hückel–Onsager theory to interionic forces. However, it is certain that the electrophoretic and relaxation effects of that theory are not the only factors influencing the mobility of an ion that conducts by a chain mechanism, and it seems probable that they may be of very little importance. It is difficult, for example, to imagine how the electrophoretic effect could apply to chain-conduction in which there is no actual movement of any individual ion. Moreover, cryoscopic measurements have shown that certainly up to concentrations of 0·5N, and probably even higher, interionic forces appear to be negligible (Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1933, **55**, 1900; and Part I).

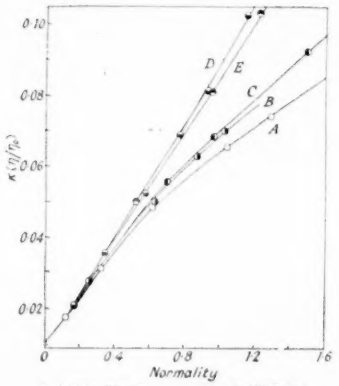
There are at least two additional factors that must influence the mobility of an ion that conducts by a chain mechanism. In discussing these we shall assume that molecular

FIG. 5. *Specific conductivities of sulphuryl chloride and trichloroacetic acid.*



lower curve, SO_2Cl_2.
upper curve, $CCl_3{\cdot}CO_2H$.

FIG. 6. *Specific conductivity–relative viscosity product for some alkali and alkaline-earth metal hydrogen sulphates.*



A, $NH_4{\cdot}HSO_4$. *D*, $Sr(HSO_4)_2$.
B, $KHSO_4$. *E*, $Ba(HSO_4)_2$.
C, $NaHSO_4$.

rotation and not proton transfer is the rate-determining process of chain conduction. Some evidence that this assumption is correct has already been presented in Part X, and additional evidence is given later. One of these additional factors arises from the solvation of the ions. The solvent molecules taking part in this solvation will be more or less tightly held by the ions, and their freedom of motion will be considerably restricted. In particular, they will less easily be able to rotate and will therefore play a correspondingly smaller part in the process of chain conduction. Alternatively, ion solvation may be said slightly to increase the average time of rotation of the sulphuric acid molecules and thus correspondingly reduce the hydrogen sulphate ion mobility. It follows that the greater the degree of solvation of the ions of the solute the smaller should be the specific conductivity of that solute at any given concentration. The hydrogen sulphate ion is common to all the solutes we are considering, and so, for the purposes of comparison, we do not need to take its solvation into account. The relative extent of solvation of the alkali and alkaline-earth metal cations has been determined by means of cryoscopic, density, and transport-number measurements (Parts I, X, and XI, *locc. cit.*), and found to be

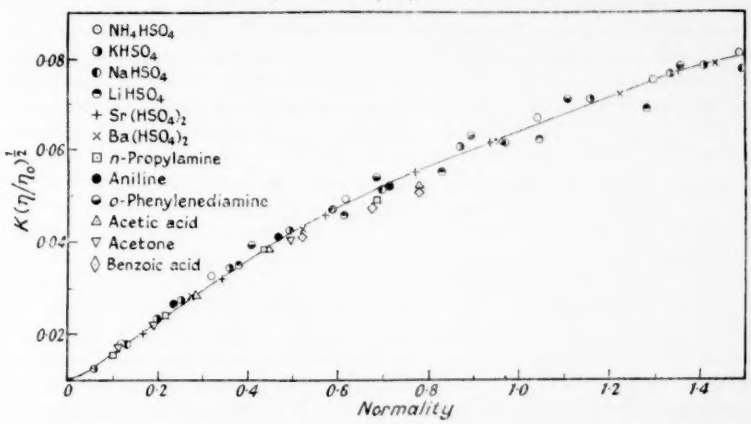
$$NH_4^+ < K^+ < Na^+ < Li^+ < Ba^{++} < Sr^{++}$$

which is also the order which would be expected on the assumption that the extent of solvation increases with increasing polarising power of the ion, and is exactly the order of decreasing conductivity of solutions of their hydrogen sulphates. As has been pointed

out in Part XI (*loc. cit.*) the varying degrees of solvation of these ions are also reflected in the viscosities of solutions of their hydrogen sulphates, the restriction of the motion of these solvent molecules taking part in solvation causing an increase in the viscosity of the solution, and the order of increasing viscosity of these solutions is exactly that of increasing solvation of the cations given above.

For normal conduction by diffusion, Stokes's law is usually assumed to hold, from which it follows that the mobility of an ion is inversely proportional to the viscosity of the solution, and this conclusion has been shown to be reasonably correct for a number of different ions and solvents. An attempt to correct our observed conductivities to allow for viscosity changes on this basis, by multiplying the specific conductivity κ by the relative viscosity η/η_0 (where η is the viscosity of the solution and η_0 that of the pure solvent), gave obviously incorrect results. As can be seen from Fig. 6, the order of the conductivities has been completely reversed and they are still all quite diffierent. However, this is not really surprising as although Stokes's law may well hold for normal conduction by diffusion, it cannot be expected to apply to conduction by the quite different chain mechanism. However, it was found that to a fair approximation the conductivity was inversely proportional to the square root of the viscosity of the solution. By plotting $\kappa(\eta/\eta_0)^{\frac{1}{2}}$ against concen-

FIG. 7. *Corrected specific conductivities.*



tration a nearly common curve was obtained for a large number of electrolytes, as shown in Fig. 7. It is not certain that this result has any fundamental significance and the relationship is in any case only approximate; but the fact that the mobility is in any way related to the viscosity provides support for the assumption that molecular rotation and not proton transfer is rate-determining, as it is difficult to see how the rate of proton transfer could be much affected by the viscosity of the medium.

The second of the additional factors that will influence the mobility of an ion that conducts by a chain mechanism arises from collisions between conducting chains. Each collision between two chains will result in a decrease in the average mobility of the chain-conducting ion. Consider the situation that arises when two hydrogen sulphate ions, each one part of a conducting chain, arrive simultaneously at positions adjacent to the same sulphuric acid molecule:

$$\begin{array}{ccc} HSO_4^- & & H_2SO_4 \\ & H_2SO_4 & \\ HSO_4^- & & H_2SO_4 \end{array}$$

One chain can pass on through the sulphuric acid molecule as soon as it becomes correctly orientated, but the other chain must wait until the sulphuric acid molecule has played its part in the first chain and then re-orientated itself to take part in the second. Thus as far as this second chain is concerned the average time of rotation of this sulphuric acid molecule has increased and the average mobility of the hydrogen sulphate ion in this chain is decreased

accordingly. The greater the concentration of hydrogen sulphate ions the more frequent will such collisions be, and hence the more will the mobility of the hydrogen sulphate ion be decreased.

Hence, the solvation effect determines a decrease of mobility of the hydrogen sulphate ion with increasing concentration which is specific for each cation, while chain collisions determine a general decrease of mobility of the hydrogen sulphate ion with increasing concentration. The general agreement of these conclusions with our exprimental results provides additional justification of our original assumption that molecular rotation is the rate-determining stage of chain conduction in sulphuric acid. It would seem to be much more difficult to account for the observed effects of different cations and of concentration on the mobility of the hydrogen sulphate ion if proton transfer were the rate-determining process.

A comparison of the equivalent conductivity values in Table 4 with some equivalent conductivities in aqueous solutions is of interest. In a 0·1N-solution in water at 25° the equivalent conductivity of hydrochloric acid is 391, of sodium hydroxide 221, and of potassium chloride 129. In sulphuric acid at 25° the equivalent conductivity of, *e.g.*, potassium hydrogen sulphate is 156, and the transport number of the potassium ion being taken as 0·03 (Table 1, Part X), this means that the equivalent conductivity of the potassium ion is approximately 5, and that of the hydrogen sulphate ion approximately 150. Thus it is not that the hydrogen sulphate ion in sulphuric acid has such an abnormally high mobility, but rather that cations such as the potassium ion have abnormally small mobilities, because of the high viscosity of sulphuric acid, which causes the transport number of the hydrogen sulphate ion to be so very near to unity. If one assumes that proton transfer is easier the stronger the hydrogen bonding in the liquid, then one would expect proton transfer to be easier in sulphuric acid than in water, and if proton transfer were the rate-determining step of chain conduction in both cases the mobility of the hydrogen and hydrogen sulphate ions in sulphuric acid would be greater than that of the hydrogen and hydroxide ions in water. The fact that the first two ions in sulphuric acid have mobilities which are quite comparable with that of the third ion in water and rather less than that of the hydrogen ion strongly suggests that, at least in sulphuric acid, proton transfer is not rate-determining. This may be attributed to the strong hydrogen bonding in the liquid hindering molecular rotation, evidence of which is given by the high viscosity of sulphuric acid. The difference in the mobilities of the hydrogen and hydroxide ions in water moreover suggests that here proton transfer is rate-determining, or at least of comparable speed to molecular rotation.

The Conductivities of Some Strong Electrolytes.—Extensive use has been made of the cryoscopic method for investigating the ionisation of solutes in sulphuric acid (cf. Parts I—VIII and references given therein). Not only does sulphuric acid have a convenient freezing point and other properties that make the experimental technique relatively simple, but the apparent ideality of the solutions considerably simplifies the interpretation of the results and enables a relatively accurate estimate of the degree of ionisation of a solute to be made. It is obvious, however, from the results so far discussed, that conductivity measurements cannot be so useful in this connection as cryoscopy has been. Whereas all electrolytes of the same valency type have almost exactly the same freezing-point depression, they may, as we have seen, have quite appreciably different conductivities. Moreover, in order to calculate equivalent or molar conductivities it is necessary to know the densities of the solutions, which involves making another measurement in addition to that of the conductivity. The assumption, that might be made for simplicity, that the densities of solutions are the same as that of the pure solvent may be only very approximately true at the relatively high concentrations at which it is necessary to work. Thus if this assumption is made it is another factor contributing towards the difference between the conductivities of electrolytes of the same valency type. Conductivity measurements can therefore only be used to differentiate between different possible modes of ionisation of a solute and not to determine exact or even approximate degrees of ionisation. Since the conductivity of any basic solute in sulphuric acid is due almost exclusively to the hydrogen sulphate ion, the information that can be obtained from a determination of the

conductivity of a solute is the number of hydrogen sulphate ions produced by the ionisation of one molecule of the solute. This may provide a useful check on conclusions drawn from a cryoscopic investigation of the ionisation of a solute, since this method enables one to find the total number of particles, both ionised and un-ionised, produced on dissolution of one molecule of the solute.

It will be convenient for our discussion to classify basic solutes in terms of the number of hydrogen sulphate ions produced by the ionisation of one molecule of the solute, and we shall therefore consider mono-, di-, tri-, and tetra-(hydrogen sulphates) in turn.

The specific conductivity curves in Figs. 2 and 3 and the molar conductivities given in Table 6 for water, acetic acid, acetone, benzoic acid, *n*-propylamine, aniline, methyl alcohol, and ethyl alcohol are sufficiently close to the corresponding specific and molecular conductivities of the alkali-metal hydrogen sulphates to justify the conclusion that one molecule of each of these solutes produces one hydrogen sulphate ion in solution. Cryoscopic measurements have shown that acetic acid and acetone (Part I) and benzoic acid (Gillespie, unpublished experiments) produce exactly two particles per molecule up to a concentration of 0·4N, suggesting that they are fully ionised according to the equation $B + H_2SO_4 = BH^+ + HSO_4^-$. The conductivity results are in full agreement with this conclusion, and show in addition that at concentrations greater than 0·4N the ionisation must still be considerable if not complete, although they provide no exact information about this.

Cryoscopic measurements (Part II) have shown that water is approximately 90% ionised in a 0·2N-solution and correspondingly less ionised at higher concentrations according to the equation $H_2O + H_2SO_4 = H_3O^+ + HSO_4^-$. The conductivity results are in agreement with this conclusion, although one could not have concluded from these alone that the ionisation was incomplete.

TABLE 6. *Molar conductivities at* 25°.

	Mono(hydrogen sulphates).*									
M	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
0·1	158	155	156	155	156	156	152	155	152	152
0·2	120	120	115	120	117	117	116	120	108	113
0·3	105	102	100	102	103	101	99·3	102	93·3	96·3
0·4	95·3	92·5	90·3	91·5	93·8	91·8	89·5	91·5	84·2	86·0
0·6	82·2	80·1	78·3	79·3	79·8	78·3	77·1	77·7	70·7	72·0
0·8	73·5	72·4	70·0	70·5	70·1	69·5	67·9	67·2	60·0	61·1
1·0	66·3	63·9	63·2	62·9	62·2	61·9	59·8	59·1	53·3	52·6

	Di(hydrogen sulphates).				Tri(hydrogen sulphate).		Tetra(hydrogen sulphate).	
M	(11)	(12)	(13)	(14)	M	(15)	M	(16)
0·05	306	300	306	304	0·033	453	0·025	616
0·10	229	229	236	21	0·066	336	0·050	454
0·15	197	—	201	179	0·100	296	0·075	388
0·20	177	—	187	150	0·133	268	0·100	349
0·30	155	—	153	132				
0·40	138	—	130	110				
0·50	125	—	119	95				

* (1) NH_4HSO_4. (2) $COMe_2$. (3) H_2O. (4) NH_2Pr^n. (5) EtOH. (6) MeOH. (7) $CH_3{\cdot}CO_2H$. (8) NH_2Ph. (9) $LiHSO_4$. (10) $Ph{\cdot}CO_2H$. (11) HNO_3. (12) $CPh_3{\cdot}OH$. (13) $o\text{-}C_6H_4(NH_2)_2$. (14) $Ba(HSO_4)_2$. (15) N_2O_4. (16) Hexamethylenetetramine.

The ionisation of *n*-propylamine and aniline was investigated by Oddo and Scandola (*Gazzetta*, 1909, **39**, i, 569), whose relatively crude cryoscopic measurements showed extensive if not complete ionisation as simple bases. Our present conductivity results are in full agreement with this conclusion.

It has been shown by cryoscopic measurements (Part VII) that methyl and ethyl alcohol each ionise according to the equation

$$ROH + 2H_2SO_4 = RHSO_4 + H_3O^+ + HSO_4^-$$

with in addition, perhaps, a very slight basic ionisation of the alkyl hydrogen sulphate

$$RSO_4H + H_2SO_4 = RSO_4H_2^+ + HSO_4^-$$

The conclusion from the conductivity results that one hydrogen sulphate ion is formed on the ionisation of one molecule of each of these alcohols is in full accord with this interpretation of the cryoscopic results.

A comparison of the molar conductivities of nitric acid, *o*-phenylenediamine, and triphenylmethanol (Table 6) with those of barium and strontium di(hydrogen sulphate) shows that all these solutes ionise to give two hydrogen sulphate ions. By cryoscopic, spectroscopic, and other methods, nitric acid has been shown to be converted into fully ionised nitronium hydrogen sulphate and almost fully ionised hydroxonium hydrogen sulphate (Gillespie and Millen, *Quart. Reviews*, 1948, **2**, 277). This can be best represented by the equation

$$HNO_3 + 2H_2SO_4 = NO_2^+ + H_3O^+ + 2HSO_4^-$$

The present conductivity results are in complete accord with this conclusion. There has been no previous study of *o*-phenylenediamine, but our results indicate that it is extensively if not completely ionised according to the equation

$$C_6H_4(NH_2)_2 + 2H_2SO_4 = [C_6H_4(NH_3)_2]^{++} + 2HSO_4^-$$

The ionisation of triphenylmethanol has been investigated cryoscopically by Hammett and Deyrup (*J. Amer. Chem. Soc.*, 1933, **55**, 1900), who found that it gave almost exactly four particles. This result has been explained as being due to the ionisation

$$Ph_3C{\cdot}OH + 2H_2SO_4 = Ph_3C^+ + H_3O^+ + 2HSO_4^-$$

with which our conductivity results are in complete agreement. It is noteworthy that although the ionisation of *o*-phenylenediamine gives rise to only three ions while nitric acid and triphenylmethanol give four ions, they all have very nearly the same conductivity. This is due, of course, to the fact that the conductivity is due almost entirely to the hydrogen sulphate ion, and two hydrogen sulphate ions result from the ionisation of each of these solutes.

The only tri(hydrogen sulphate) that we have investigated is dinitrogen tetroxide which has been found cryoscopically (Part III) to give nearly six particles and has therefore been assumed to ionise according to the equation

$$N_2O_4 + 3H_2SO_4 = NO^+ + NO_2^+ + H_3O^+ + 3HSO_4^-$$

The fact that the values of its molar conductivity are greater than those for the di(hydrogen sulphates) and are in fact to quite a good approximation three times those for the mono(hydrogen sulphates) at the same hydrogen sulphate ion concentrations provides further support for the above mode of ionisation for dinitrogen tetroxide.

Hexamethylenetetramine does not appear to have been previously investigated. It has molar conductivity values that are greater again than those for dinitrogen tetroxide and are approximately four times the average values for a mono(hydrogen sulphate), strongly suggesting that four hydrogen sulphate ions result from its ionisation, which may accordingly be represented by the equation

$$C_6H_{12}N_4 + 4H_2SO_4 = [C_6H_{12}N_4H_4]^{4+} + 4HSO_4^-$$

At the present stage of our knowledge of solutions in sulphuric acid, little can be said about the differences between the conductivities of the organic mono(hydrogen sulphates), the only class of organic compounds that we have studied at all extensively. If we can discount the possibility that organic solutes have some specific effect which causes an increase in the mobility of the hydrogen sulphate ion, then it would appear from a comparison with the molar conductivities of ammonium and lithium hydrogen sulphates that the cations of all the solutes we have studied are more solvated than the ammonium ion and less solvated than the lithium ion. This conclusion is in fair agreement with that drawn from the results of cryoscopic measurement (Part I), *viz.*, that the ammonium ion and the cations of acetone and acetic acid all have solvation numbers of approximately unity. It is possible, however, that the disruption of the structure of the sulphuric acid

by large organic cations enables some sulphuric acid molecules to rotate more easily, and thus increases the mobility of the hydrogen sulphate ion.

The Conductivities of Some Weak Electrolytes and Some Non-electrolytes.—We have investigated the conductivities of solutions of three solutes, *p*-nitrotoluene, disulphuric acid, and dichloroacetic acid, that have been shown by cryoscopy to behave as weak electrolytes (Hantzsch, *loc. cit.*; and Parts II and VII). The results of these measurements have been given in Table 3 and in Fig. 4. No values for the molar conductivities of these solutes have been given, for up to almost the highest concentrations we have investigated, particularly in the cases of disulphuric acid and dichloroacetic acid, the repression of the autoprotolysis of the solvent is appreciably incomplete. Moreover, as already pointed out, such values would be of little use since, in view of the differences between the conductivities of solutes that are known to be fully ionised, they could only be used to calculate approximate degrees of ionisation. It is probably justifiable to conclude from the conductivity–concentration curves in Fig. 4 that the extent of ionisation of these solutes increases in the order dichloroacetic acid < disulphuric acid < *p*-nitrotoluene, which is in agreement with the results of the cryoscopic measurements. Hantzsch (*loc. cit.*) showed that dichloroacetic acid is approximately 20% ionised in roughly the same concentration range as we have used, and in Part VII it was shown that *p*-nitrotoluene is 73% ionised in a 0·1m-solution. The ionisation of disulphuric acid is slightly complicated by the formation of higher polysulphuric acids, such as trisulphuric acid ($H_2S_3O_{10}$), but if this complication is ignored, cryoscopic measurements show that disulphuric acid is 38% ionised in a 0·1m-solution. It is justifiable to compare the acidic solute disulphuric acid with the two basic solutes, for it has been shown in Part IX that the mobility of the hydrogen ion ($H_3SO_4^+$) is very nearly if not exactly equal to that of the hydrogen sulphate ion.

Solutions of non-electrolytes in sulphuric acid will of course have a conductivity due to the hydrogen and hydrogen sulphate ions arising from the autoprotolysis of the solvent. We have investigated two solutes that have been regarded from freezing-point depression measurements as behaving as non-electrolytes, *viz.*, sulphuryl chloride, studied by Gillespie, Hughes, and Ingold (Part I), and trichloroacetic acid, studied by Hantzsch (*loc. cit.*) and by Hammett and Deyrup (*J. Amer. Chem. Soc.*, 1933, **55**, 1900). A number of other solutes which were regarded by Hantzsch and by Hammett and Deyrup as behaving as non-electrolytes have been shown cryoscopically to be weak electrolytes (Parts I and VII). The results of our experiments with these two solutes have been given in Table 3 and Fig. 5. It may be seen that in both cases the conductivity of the solution decreases slightly with increasing concentration of the solute. Such a decrease in conductivity would be expected because of the dilution of the conducting sulphuric acid by the non-conducting solute. If this were the only effect operating to reduce the conductivity of the solution, the specific conductivity should decrease linearly with the molarity of sulphuric acid in the solution with a slope of $\kappa_0/c_0 = 5{\cdot}55 \times 10^{-4}$, where κ_0 is the specific conductivity of pure sulphuric acid and c_0 its molarity (lower curve on Fig. 5). In fact, as may be seen from Fig. 5, the specific conductivity does decrease linearly with the molarity of sulphuric acid in the case of sulphuryl chloride, although the slope of the straight line is considerably greater, namely, $9{\cdot}2 \times 10^{-4}$. This additional decrease in the specific conductivity may be attributed either to a decrease in the extent of autoprotolysis of the solvent owing to a decreased ionising power or dielectric constant of the solution, or to a decrease in the mobility of the hydrogen or hydrogen sulphate ions, or to both. The specific conductivity of solutions of trichloroacetic acid does not decrease linearly with the molarity of sulphuric acid, and at all concentrations the conductivities are slightly greater than those for sulphuryl chloride. This may be due either to a different effect of trichloroacetic acid on the extent of autoprotolysis or on the mobility of the hydrogen and hydrogen sulphate ions, or to a very slight ionisation of trichloroacetic acid as a base. In view of the basic properties of dichloroacetic acid, it is not unreasonable to suppose that trichloroacetic acid will also be basic if only to a very limited extent.

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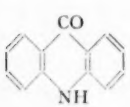
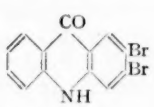
47. *The Bromination of Acridone.*

By R. M. Acheson and M. J. T. Robinson.

Re-investigation of the bromination of acridone has shown that the product is not 2 : 3-dibromoacridone as claimed by Tanasescu and Ramontianu (*Bull. Soc. chim.*, 1939, **6**, 486) but 3 : 7-dibromo- or 1 : 3 : 7 : 9-tetrabromoacridone according to the conditions. The structures of these bromoacridones have been proved by their identity with authentic specimens prepared by the cyclisation of diphenylamine-2-carboxylic acids. Vigorous bromination of 1 : 3 : 7 : 9-tetrabromoacridone gives an unidentified hexabromoacridone.

Although the nitration and sulphonation of acridone (I) have been fairly extensively investigated (Lehmstedt, *Ber.*, 1931, **64**, 2381; Matsumura, *J. Amer. Chem. Soc.*, 1935, **57**, 1533), little work has been done on the halogenation of acridone or its derivatives. Eckert and Steiner (*Sitzungsber. Akad. Wiss. Wien*, 1914, **123**, 1141) obtained octachloroacridone from acridone and 10-methylacridone and antimony pentachloride, and Tanasescu and Ramontianu (*loc. cit.*) have examined the chlorination of 10-hydroxyacridone and acridone, and claim that the bromination of acridone and 10-hydroxyacridone under conditions which they do not define gives the 2 : 3-dibromo-compounds (*e.g.*, II). Bromination of "3-chloro-," and 10-hydroxy-2-nitroacridone effects only monosubstitution, which led these authors to claim that the disubstitution product obtained from acridone was (II), as


(I)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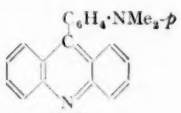
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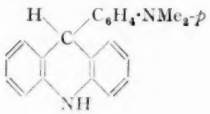
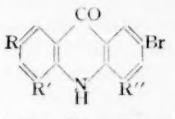

(IV)

in the other cases they considered the nitro- or chloro-group to occupy one of the substitutable positions. This argument is open to many objections. A chloro-, bromo-, or nitro-substituent, irrespective of position, will deactivate the substituted ring so that the bromine is expected to attack the unsubsituted ring first. The structure of the supposed "3-chloro-10-hydroxyacridone" is incorrect; Lehmstedt (*Ber.*, 1932, **65**, 834) showed that the substance is 2-chloro-10-hydroxyacridone. It is also difficult to explain why the bromine should attack position 2 when nitration, which presumably proceeds through a similar cationoid attack, causes substitution only at positions 1, 3, 7, and 9.

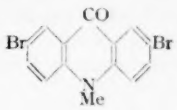
The bromination was therefore re-investigated. The general technique was to compare the products of bromination with bromoacridones of definite constitution. Direct mixed-melting point determinations were not suitable for this as the melting points are, with one exception, too high; the acridones were therefore converted into the lower-melting 5-chloroacridines with phosphorus oxychloride alone, or with the addition of a dialkylaniline into the 5-dialkylaminophenylacridines (*e.g.*, III). Gilman and Shirley (*J. Amer. Chem. Soc.*, 1950, **72**, 2181) have provided the only structural proof of (III) by its synthesis from (IV). The comparatively low-melting 5-*p*-dialkylaminophenylacridines have been recommended for the characterisation of acridones by Albert ("The Acridines," Arnold, 1950, p. 133) but this is now endorsed only if the original acridone is comparatively pure. Mixtures of these derivatives, prepared from inseparable mixtures of brominated acridones, could not be resolved by crystallisation in any case examined, as mixed crystals or lattice compounds were formed. Tedious chromatographic separations are necessary in order to separate sufficient quantities of pure materials from such mixtures for identification. Fractionation of the corresponding 5-chloroacridines appears to be preferable.

The brick-red precipitate obtained when bromine was added to a cold solution of acridone in acetic acid became yellow when warmed, kept, or treated with water or bases. It could not be obtained free from acetic acid, but an estimate of the "available bromine" was obtained in sulphuric–acetic acid solution by titration of the iodine liberated from potassium iodide. Somewhat less than half the original bromine was "available," so the

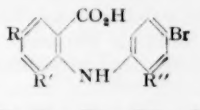
precipitate appeared to contain perbromides. 10-Bromoacridones are probably absent, as 10-methylacridone gives a similar red substance. When the acridone–bromine–acetic acid mixture was heated to 60—70° the red precipitate became yellow and gave a mixture of acridones which could not be separated by crystallisation before or after conversion into the corresponding 5-dialkylaminophenylacridines; in one instance the resulting mixture of acridines melted sharply at 238°, unchanged by recrystallisation. Authentic 3-bromo-5-*p*-dimethylaminophenylacridine also has m. p. 238° but a mixture melted at 217°. The formation of 3-bromoacridone (V) in the bromination of acridone was, however, proved by a tedious chromatographic separation of the mixed 5-dimethylaminophenylacridines on alumina. As only one orange band is formed colour reactions were devised, with pure acridines, whereby the elution of 3-bromo-5-*p*-dimethylaminophenylacridine could be detected; this compound was eventually isolated in a pure condition. 3 : 7-Dibromoacridone was also shown present in the bromination product by reaction with phosphorus oxychloride followed by fractional crystallisation of the resulting 5-chloroacridines; it was not possible to obtain pure 3-bromo-5-chloroacridine from this fractionation.



(V; R = R′ = R″ = H)
(VI; R = Br, R′ = R″ = H)
(VII; R = R′ = Br, R″ = H)
(VIII; R = R′ = R″ = Br)



(IX)



(X; R = R′ = R″ = H)
(XI; R = Br, R′ = R″ = H)
(XII; R = R′ = Br, R″ = H)
(XIII; R = R′ = R″ = Br)

Boiling acridone with bromine in acetic acid gives an excellent yield of 3 : 7-dibromoacridone (VI), proved identical with the cyclisation product of 4 : 4′-dibromodiphenylamine-2-carboxylic acid (XI) by comparison of lower-melting derivatives. Since the completion of this work Kruger (*J.*, 1952, 3648) prepared 3 : 7-dibromoacridone from the corresponding diamine, and showed it identical with an acridone bromination product by a comparison of the corresponding 5-diethylaminophenylacridines.

Further bromination of 3 : 7-dibromoacridone yields inseparable mixtures unless the reaction is continued until 1 : 3 : 7 : 9-tetrabromoacridone (VIII), best prepared by refluxing acridone with a large excess of bromine in acetic acid, is formed. Formation of 1 : 3 : 7-tribromoacridone (VII) in the bromination of 3 : 7-dibromoacridone (VI) can be shown if the reaction time is insufficient for tetrasubstitution. The least soluble fraction of the mixed bromoacridones in *m*-cresol was heated to 100° with phosphorus oxychloride and diethylaniline to convert all the unchanged 3 : 7-dibromoacridone into 3 : 7-dibromo-5-*p*-diethylaminophenylacridine. Impure 1 : 3 : 7-tribromo-5-chloroacridine remained after extraction with hot dilute acid, and after much purification proved identical with a specimen of known structure. The last separation depends on the fact that although acridone and its 3-bromo-, and 3 : 7-dibromo-, and many other derivatives will give the corresponding 5-dialkylaminophenylacridines with dialkylanilines and phosphorus oxychloride during 2 hours at 100°, 1 : 3 : 7-tribromo- and 1 : 3 : 7 : 9-tetrabromo-acridone give only the 5-chloroacridines under these conditions. These 5-chloroacridines nevertheless react readily with dimethyl- or diethyl-aniline in the presence of aluminium chloride (Drozdov, *Chem. Abstracts*, 1937, **31**, 4321) to give the corresponding 5-dialkylaminophenylacridines.

Further bromination of 1 : 3 : 7 : 9-tetrabromoacridone could only be effected in boiling bromine in the presence of aluminium bromide. An unidentified 1 : 3 : 7 : 9 : *x* : *x*-hexabromoacridone was formed and further substitution did not appear to take place.

10-Methylacridone readily gave 3 : 7-dibromo-10-methylacridone (IX), prepared also by the methylation of 3 : 7-dibromoacridone, with a small excess of bromine in boiling acetic acid. Only 1 : 3 : 7 : 9-tetrabromoacridone (VIII) could be isolated from a more vigorous bromination; demethylation is not unexpected by analogy with the results of Eckert and Steiner (*loc. cit.*).

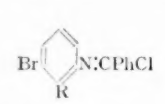
These results show that the structures given by Tanasescu and Ramontianu to many

of their halogenated acridones are erroneous, their "2 : 3-" disubstituted derivatives being 3 : 7-derivatives, etc.

The acridones and their derivatives of known structure required for comparison were prepared from the appropriate diphenylamine-2-carboxylic acids or their derivatives. *p*-Bromoaniline with 2-chloro- and 5-bromo-2-chloro-benzoic acid gave, by the Ullmann reaction, 4'-bromo- (X) (Ullmann and Tedescu, *Annalen*, 1907, **355**, 351) and 4 : 4'-dibromodiphenylamine-2-carboxylic acid (XI). The latter could not be prepared from *p*-dibromobenzene and 5-bromoanthranilic acid. Refluxing phosphorus oxychloride cyclised both these acids to 5-chloroacridines, which with diethyl- and dimethyl-aniline gave the corresponding dialkylaminophenylacridines also required for comparison purposes.

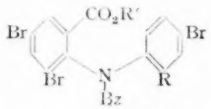
Attempts were also made to prepare the tri- and tetra-bromo-acids (XII and XIII) by the Ullmann condensation. 3 : 5-Dibromoanthranilic acid (Freundler, *Compt. rend.*, 1909, **149**, 1137), in a Sandmeyer reaction, gave an excellent yield of 3 : 5-dibromo-2-chlorobenzoic acid. Unfortunately only reductive dehalogenation (cf. Goldberg and Kelly, *J.*, 1946, 102) to 3 : 5-dibromobenzoic acid took place when this acid was used in Ullmann condensations with 4-bromo- and 2 : 4-dibromo-aniline.

Jamison and Turner's adaptation (*J.*, 1937, 1954) of Chapman's diphenylamine synthesis (*J.*, 1927, 1743) is the only method available for the preparation of 1 : 3 : 7-tribromoacridone (VII), and is satisfactory in the case of 1 : 3 : 7 : 9-tetrabromoacridone (VIII)



(XIV; R = H)
(XV; R = Br)

(XVI; R = H)
(XVII; R = Br)



(XVIII; R = H, R' = Me)
(XIX; R = Br, R' = Me)
(XX; R = R' = H)

2' : 4'-Dibromobenzanilide, prepared by the bromination of benzanilide, and 4'-bromobenzanilide with phosphorus pentachloride gave the imidoyl chlorides (XV and XIV). These chlorides and the sodium derivative of methyl 3 : 6-dibromosalicylate gave the imidates (XVII and XVI) which at >200° rearranged to the methyl *N*-benzoyldiphenylamine-2-carboxylates (XIX and XVIII); neither the imidate nor its rearrangement product in the tetrabromo-series could be obtained crystalline. Pyrolysis of (XX), obtained by the partial hydrolysis of (XVIII), gave an excellent yield of 1 : 3 : 7-tribromoacridone (VII) (cf. Jamison and Turner, *loc. cit.*) but the simplest way of cyclising the *N*-benzoyl esters is by sulphuric acid at 160—200° : excellent yields of (VII and VIII) are thus obtained.

Methyl 3 : 5-dibromosalicylate was easily prepared by the iron-catalysed bromination of methyl salicylate, although this bromination is stated (Cahours, *Annalen*, 1894, **52**, 328; Kaufmann and Egner, *Ber.*, 1913, **46**, 3786) to give mixtures. Bromination of salicylic acid, contrary to previous reports (Robertson, *J.*, 1902, **81**, 1480; Leulier and Pinet, *Bull. Soc. chim.*, 1927, **41**, 1367), gave much 3-bromosalicylic acid and 2 : 4 : 6-tribromophenol as well as 3 : 5-dibromosalicylic acid.

Experimental

5-p-*Dialkylaminophenylacridines.*—*Method* 1. The acridone (1·0 g.), phosphorus oxychloride (2 ml.), and dimethyl- or diethyl-aniline (4 ml.) were heated to 100° (2—3 hr.), diluted with water (100 ml.), and basified and excess of amine was removed by steam. The residual solid was passed in benzene through a short alumina column, and recovered from the eluate.

Method 2. When method 1 was carried out on a very small scale the reaction product was dissolved in boiling 2N-hydrochloric acid and filtered into excess of aqueous sodium acetate, and the precipitate purified as before.

Method 3. The 5-chloroacridine (0·02—0·2 g.), aluminium chloride (0·1—0·5 g.), and dimethyl- or diethyl-aniline (1—2 ml.) were heated at 100° (4—6 hr.). The product was boiled with 2N-hydrochloric acid (20 ml.), and the yellow or orange residue collected, washed with hot dilute acid, water, and concentrated aqueous ammonia, dried, and chromatographed.

Detection of **3-Bromoacridone** (V).—Bromine (1·64 g.) in acetic acid (20 ml.) was added to a cold solution of acridone (2·0 g.) in acetic acid (300 ml.), and the mixture left at room temperature until the bulky red solid immediately precipitated had become yellow. A clear solution was obtained on boiling and deposited microscopic yellow needles (1·4 g.) when cold. This mixture of acridones was converted into the corresponding 5-*p*-dimethylaminophenylacridines (method 1), which (0·7 g.) were adsorbed on alumina from a saturated solution in light petroleum (1 l., b. p. 60—80°). A single orange band was formed and eluted with light petroleum (b. p. 60—80°)–benzene (3 : 1). No visual separation of the mixture was observed, but when the colour reactions of the eluate indicated the presence of mainly 3-bromo-5-*p*-dimethylaminophenylacridine this was collected and evaporated. Repeated crystallisation of the residue from benzene, followed by ethanol, gave 3-bromo-5-*p*-dimethylaminophenylacridine as yellow needles, m. p. 237·5° alone or mixed with an authentic specimen (m. p. 239°) (Found: C, 66·6; H, 4·5. Calc. for $C_{21}H_{17}N_2Br$: C, 66·8; H, 4·5%).

A portion of the mixed bromoacridones with refluxing phosphorus oxychloride gave the 5-chloroacridines which after chromatographic purification (benzene–alumina) and fractional crystallisation from benzene–light petroleum (b. p. 60—80°) gave **3 : 7-dibromo-5-chloroacridine** as the least soluble fraction, m. p. 218° alone or mixed with an authentic specimen. A more soluble fraction, m. p. 128—130°, appeared to be substantially 3-bromo-5-chloroacridine, m. p. 134—135°, mixed m. p. 130—133°.

3 : 7-*Dibromoacridone* (VI).—A mixture of bromine (4·1 g.), acridone (2·0 g.), and acetic acid (250 ml.) was boiled until the flocculent yellow precipitate became granular (10 min.), then filtered hot, and the residual yellow solid (2·4—2·8 g., 70—80%) washed with hot acetic acid. On crystallisation from *m*-cresol **3 : 7-*dibromoacridone*** was obtained (80%) as yellow needles, m. p. > 340° (Found: C, 44·2; H, 2·3; Br, 44·3. $C_{13}H_7ONBr_2$ requires C, 44·3; H, 2·0; Br, 45·2%). **3 : 7-*Dibromo*-5-p-*dimethylaminophenylacridine*** (method 2) crystallised from ethanol in yellow granules, m. p. 271—272°, and mixed m. p. 272° with an authentic specimen of m. p. 273—273·5° (Found: C, 55·5; H, 3·4. $C_{15}H_{16}N_2Br_2$ requires C, 55·3; H, 3·5%). **3 : 7-*Dibromo*-5-p-*diethylaminophenylacridine***, similarly prepared and purified, separated from ethanol in yellow plates, m. p. 274° alone or mixed with an authentic specimen (m. p. 274°) (Found: C, 57·4; H, 4·6. $C_{23}H_{20}N_2Br_2$ requires C, 57·0; H, 4·6%).

Detection of **1 : 3 : 7-*Tribromoacridone*** (VII).—**3 : 7-Dibromoacridone** (5·9 g.), bromine (2·5 ml.), and acetic acid (50 ml.) were refluxed for 2·5 hours and the yellow solid (7·6 g.) was collected. It dissolved in boiling *m*-cresol (50 ml.) but from the refluxing solution yellow crystals separated during 1 hour. They were collected from the boiling solution, washed with acetic acid, and dried (2·5 g.). **3 : 7-Dibromoacridone** was removed by treating this solid (0·5 g.) with diethylaniline and phosphorus oxychloride (2 hours at 100°) and extracting the product with hot 2N-hydrochloric acid. The residue (0·26 g.) was purified chromatographically, and repeated crystallisation from benzene then gave **1 : 3 : 7-*tribromo*-5-*chloroacridine*** as yellow needles, m. p. 232—233°, which did not depress the m. p. of an authentic specimen (Found: C, 34·9; H, 1·3. $C_{13}H_5ClNBr_3$ requires C, 34·7; H, 1·1%. **1 : 3 : 7-*Tribromo*-5-p-*dimethylaminophenylacridine*** (method 3) separated from benzene–ethanol as scarlet prisms, the less common crystal form, of m. p. 292—293° alone or mixed with an authentic specimen (Found: C, 47·2; H, 2·8. $C_{21}H_{15}N_2Br_3$ requires C, 47·2; H, 2·9%). **1 : 3 : 7-*Tribromo*-5-p-*diethylaminophenylacridine*** (method 3) crystallised from benzene–ethanol in orange-red prisms, m. p. 260·5° alone or mixed with authentic specimen (Found: C, 48·8; H, 3·4; Br, 42·1. $C_{23}H_{19}N_2Br_3$ requires C, 49·1; H, 3·4; Br, 42·5%).

1 : 3 : 7 : 9-*Tetrabromoacridone* (VIII).—Acridone (1·0 g.), bromine (10 ml., in two portions, the second after 6 hours), and acetic acid (50 ml.) were refluxed for 18—24 hours and the precipitate was collected, washed, and dried (m. p. 307—308°; 2·1—2·2 g.). On crystallisation from *m*-cresol–acetic acid **1 : 3 : 7 : 9-*tetrabromoacridone*** was obtained in pale yellow needles, m. p. 308—308·5° alone or mixed with an authentic specimen (Found: C, 30·6; H, 1·3; Br, 62·2. $C_{13}H_5ONBr_4$ requires C, 30·6; H, 1·0; Br, 62·5%).

1 : 3 : 7 : 9-*Tetrabromo*-5-*chloroacridine*.—This *acridine*, prepared from the acridone with phosphorus oxychloride, separated from benzene in pale yellow needles which rapidly changed to thick lemon-yellow prisms, m. p. 254—254·5°, unchanged on admixture with an authentic specimen (Found: C, 29·6; H, 0·8; Hal., 66·3. $C_{13}H_4ClNBr_4$ requires C, 29·5; H, 0·8; Hal., 67·2%). **1 : 3 : 7 : 9-*Tetrabromo*-5-p-*dimethylaminophenylacridine*** (method 3) separated from benzene–ethanol in bright red needles, m. p. 309—310°, or m. p. 309° on mixture with an authentic specimen (Found: C, 41·1; H, 2·2; Br, 52·2. $C_{21}H_{14}N_2Br_4$ requires C, 41·1; H, 2·3; Br, 52·1%). **1 : 3 : 7 : 9-*Tetrabromo*-5-p-*diethylaminophenylacridine*** (method 3) separated

from benzene as orange-red needles, m. p. 268° unchanged on admixture with an authentic specimen (Found : C, 43·0; H, 3·0; Br, 50·4. $C_{23}H_{18}N_2Br_4$ requires C, 43·0; H, 2·8; Br, 49·8%).

1 : 3 : 7 : 9 : x : x-*Hexabromoacridone*.—Thin aluminium foil (0·27—0·55 g.) was added in very small pieces to a mixture of acridone (1·0 g., 1 mol.) or 1 : 3 : 7 : 9-tetrabromoacridone (2·52 g., 1 mol.) and bromine (10 ml.), and the mixture refluxed for 2·5 hours to 5 days. Excess of bromine was then removed at 100° and the residual clear red gum treated with 2N-hydrochloric acid (50 ml.) with cooling. The bright yellow precipitate was collected, washed with hydrochloric acid, and dried (m. p. 346—347°; 3·35—3·42 g.), and on crystallisation from *m*-cresol gave **1 : 3 : 7 : 9 : x : x-*hexabromoacridone*** as yellow prisms, m. p. 347° (Found : C, 23·8; H, 0·7. $C_{13}H_3ONBr_6$ requires C, 23·3; H, 0·4%).

Bromination of **10-*Methylacridone*.**—(*a*) Bromine (0·9 g.) in acetic acid (11 ml.) was added to a hot solution of 10-methylacridone (0·5 g.) and sodium acetate (anhyd., 0·5 g., 2·5 mol.), and the mixture boiled gently until the flocculent yellow precipitate changed to yellow needles (5—10 min.). After cooling, **3 : 7-*dibromo*-10-*methylacridone*** was collected, washed, dried (0·71 g.), and crystallised from ethanol as very pale yellow needles, m. p. 282—283° alone or mixed with an authentic specimen (Found : C, 46·0; H, 2·4; Br, 42·7. $C_{14}H_9ONBr_2$ requires C, 45·8; H, 2·5; Br, 43·6%).

(*b*) 10-Methylacridone (0·5 g.), anhydrous sodium acetate (8·0 g.), bromine (10 ml., in two portions, the second being added after 6 hr.), and glacial acetic acid (50 ml.) were refluxed (18 hr.), and the product (0·7 g.) was precipitated with water. Crystallisation from *m*-cresol gave **1 : 3 : 7 : 9-tetrabromoacridone**, discoloured needles, m. p. 307—308°, mixed m. p. 308°.

***5-Bromo-2-chlorobenzoic Acid*.**—5-Bromoanthranilic acid (10·9 g.) was diazotised (sodium nitrite, 5·0 g.) in hydrochloric acid (8N; 120 ml.) at 5—10°, and the solution poured into cuprous chloride (6·0 g.) in hydrochloric acid (40 ml.; *d* 1·16), and after 30 minutes at 18°, the precipitate was collected. Acidification of its solution in alkali (charcoal) precipitated 5-bromo-2-chlorobenzoic acid (10·0 g.), colourless needles (from water), m. p. 155—156° (Cohen and Raper, *J.*, 1904, **85**, 1267, give this m. p.).

4 : 4′-*Dibromodiphenylamine*-2-*carboxylic Acid*.—5-Bromo-2-chlorobenzoic acid (4·7 g.), *p*-bromoaniline (6·9 g.), potassium carbonate (5·5 g.), and " Naturkupfer C " (Kahlbaum, 0·1 g.) were refluxed in amyl alcohol (15 ml.) for 5 hours. The residue from steam-distillation was extracted with ether, decolorised with charcoal, partly acidified, boiled, and filtered into an excess of hydrochloric acid. The precipitated **4 : 4′-*dibromodiphenylamine*-2-*carboxylic acid*** (4·0 g.) after one crystallisation from light petroleum (b. p. 60—80°) separated from benzene as yellow crystals, m. p. 232—234 (Found : N, 4·1. $C_{13}H_9O_2NBr_2$ requires N, 3·8%).

3-*Bromo*- and 3 : 7-*Dibromo*-5-p-*dialkylaminophenylacridine*.—4′-Bromodiphenylamine-2-carboxylic acid (X) (Ullmann and Tedescu, *Annalen*, 1907, **355**, 341) or 4 : 4′-dibromodiphenylamine-2-carboxylic acid (2·0 g.) was refluxed with phosphorus oxychloride (10 ml.) until hydrogen chloride was no longer evolved (1—2 hr.), dimethyl- or diethyl-aniline (4 ml.) added, refluxing continued for a further hour, and the product worked up as in method 1. The products, all formed in excellent yield, were crystallised once from amyl alcohol and twice from ethanol. 3-Bromo-5-*p*-dimethylaminophenylacridine separated as yellow laths, m. p. 239° (Polaczek, *Roczniki Chem.*, 1936, **16**, 76, gives m. p. 239—240°). **3 : 7-*Dibromo*-5-p-*dimethylaminophenylacridine*** formed almost cubic yellow granules, m. p. 273—273·5° (Found : C, 55·5; H, 3·8; Br, 35·3%). Red, and violet-blue colours, which are discharged on shaking, are formed with 3-bromo- and 3 : 7-dibromo-5-*p*-dimethylaminophenylacridine respectively on treatment of their solutions in benzene (0·1 ml.)–amyl alcohol (0·5 ml.) with 2N-aqueous hydrochloric acid (1 ml.). **3-*Bromo*-5-p-*diethylaminophenylacridine*** separated in orange-yellow prisms, m. p. 211° (Found : C, 68·4; H, 5·1; Br, 19·8. $C_{23}H_{21}N_2Br$ requires C, 68·2; H, 5·2; Br, 19·7%). **3 : 7-*Dibromo*-5-p-*diethylaminophenylacridine*** crystallised in minute yellow plates, m. p. 274° (Found : C, 56·7; H, 4·4; Br, 33·8%).

3-*Bromo*-5-*chloroacridine*.—4′-Bromodiphenylamine-2-carboxylic acid (X) on cyclisation with boiling phosphorus oxychloride gave 3-bromo-5-chloroacridine, which separated from benzene–light petroleum (b. p. 60—80°) in pale yellow needles, m. p. 134—185° (*Chem. Zentr.*, 1936, 4466, gives m. p. 136°).

3 : 7-*Dibromo*-5-*chloroacridine*.—This ***acridine***, prepared from the acridone with phosphorus oxychloride, separated from light petroleum (b. p. 60—80°) in pale yellow needles, m. p. 219° (Found : C, 42·1; H, 1·7. $C_{13}H_6NClBr_2$ requires C, 42·1; H, 1·6%).

3 : 7-*Dibromo*-10-*methylacridone*.—3 : 7-Dibromoacridone (1·0 g.), potassium hydroxide (3·0 g.), water (2 ml.), and ethanol (10 ml.) were heated with stirring until pasty. After cooling,

the bright greenish-yellow solid was collected and dried for 2 hours at 150°. It was then powdered and heated with methyl sulphate (3—4 ml.) at 100° for 1 hour, and after the addition of concentrated aqueous ammonia the pale yellow precipitate was collected (0·94 g., 90%). Crystallisation from ethanol gave 3 : 7-dibromo-10-methylacridone as pale yellow needles, m. p. 284° alone or mixed with a specimen prepared from 10-methylacridone (see above).

3 : 5-*Dibromo-2-chlorobenzoic Acid.*—3 : 5-Dibromoanthranilic acid (17·25 g.) suspended in hydrochloric acid (10N; 100 ml.) was diazotised (5—10°) with sodium nitrite (5·5 g.) and, after addition of urea (3 g.), poured into hydrochloric acid (50 ml.; 10N) containing cuprous chloride (6·4 g.). After 30 minutes the 3 : 5-dibromo-2-chlorobenzoic acid was collected and purified through hot aqueous alkali (charcoal); the *acid* (15·6 g.) separated from ethanol–water in colourless needles, m. p. 189—189·5° (Found: C, 27·3; H, 1·2. $C_7H_3O_2ClBr_2$ requires C, 26·8; H, 1·0%). The *amide* separated from aqueous ethanol as needles, m. p. 213—215° (Found: N, 4·2. $C_7H_2ONClBr_2$ requires N, 4·5%).

Unsuccessful Ullmann Condensations.—3 : 5-Dibromo-2-chlorobenzoic acid (8·0 g.), potassium carbonate (4·2 g.), 2 : 4-dibromoaniline (11·7 g.), and Fauconau's copper (0·1 g.; Fauconau, *Bull. Soc. chim.*, 1937, **4**, 58) were refluxed in *cyclo*hexanol (15 ml.) for 5 hours. The reaction product yielded 3 : 5-dibromobenzoic acid as needles, m. p. 214—215°, from ethanol; the amide crystallised from aqueous ethanol as needles, m. p. 185—186°. Cohen and Dutt (*J.*, 1914, **105**, 502) give m. p. 213—214° for the acid, and Sudborough (*J.*, 1895, **87**, 594) gives m. p. 187° for the amide. 3 : 5-Dibromobenzoic acid was the sole product obtained from 3 : 5-dibromo-2-chlorobenzoic acid, *p*-bromoaniline, potassium carbonate, and Naturkupfer C in either nitrobenzene or *cyclo*hexanol, with or without potassium iodide.

Methyl 3 : 5-*Dibromosalicylate.*—Bromine (77 ml.) in chloroform (100 ml.) was added to a mixture of methyl salicylate (64 ml.), chloroform (200 ml.), and iron powder (4 g.) with shaking so that a vigorous evolution of hydrogen bromide took place (5—10 min.). When the reaction slackened the mixture was refluxed from a steam-bath until the bromine vapour evolved contained only little hydrogen bromide (30—45 min.). After cooling, the semi-solid mass was shaken with sodium hydrogen sulphite (60 g.) in water (300 ml.) until almost colourless, and then washed by decantation with fresh aqueous bisulphite (10 g., in 500 ml. of water), followed by water. The heated mixture was then treated with boiling chloroform (300—400 ml.), and extraneous water removed in a heated separating funnel; on cooling, the filtered chloroform solution deposited methyl 3 : 5-dibromosalicylate as colourless prisms, m. p. 150—152° (105 g.). Repeated recrystallisation from ethanol raised the m. p. to 153° (recorded values are 148° to 156°).

N-p-*Bromophenylbenzimidoyl Chloride.*—4′-Bromobenzanilide (44 g.) and powdered phosphorus pentachloride (36 g.) were heated on a steam-bath (30 min.). Phosphorus oxychloride was removed *in vacuo*, and the residue treated with light petroleum (b. p. 60—80°; sodium-dried), which was then distilled off to remove the last traces of phosphorus chlorides. The residue was refluxed with more light petroleum (300 ml.; b. p. 60—80°) for 30 min., and the solution decanted from insoluble material and cooled to 0°. N-p-*Bromophenylbenzimidoyl chloride* separated as needles, m. p. 70° (39 g.) (Found: C, 52·7; H, 3·4; Hal., 40·0. $C_{13}H_9NClBr$ requires C, 53·0; H, 3·1; Hal., 39·2%).

Methyl N-*Benzoyl*-4 : 6 : 4′-*tribromodiphenylamine*-2-*carboxylate.*—4 : 6-Dibromo-2-carbomethoxyphenyl *N*-*p*-bromophenylbenzimidate (30 g.) rearranged to the diphenylamine at 200—210° (Jamison and Turner, *loc. cit.*, give 270°). The diphenylamine was obtained as colourless needles, m. p. 132—134° (86—94%) when the glassy reaction product crystallised from ethanol, and gave the acid, m. p. 218·5°, on mild alkaline hydrolysis.

1 : 3 : 7-*Tribromoacridone.*—(*a*) *N*-Benzoyl-4 : 6 : 4′-tribromodiphenylamine-2-carboxylic acid (5·0 g.) was heated at 300—350° and the product boiled with aqueous sodium hydroxide followed by water. It gave 1 : 3 : 7-tribromoacridone as pale yellow needles (from *m*-cresol), m. p. >340° (2·17 g.) (Found: C, 36·6; H, 1·8. Calc. for $C_{13}H_6ONBr_3$: C, 36·3; H, 1·4%). (*b*) Methyl *N*-benzoyl-4 : 6 : 4′-tribromodiphenylamine-2-carboxylate (1·0 g.) was heated with concentrated sulphuric acid (2·0 ml.) to 160—200°; on cooling, 1 : 3 : 7-tribromoacridone (0·66 g.) was precipitated.

1 : 3 : 7-*Tribromo*-5-*chloroacridine.*—1 : 3 : 7-Tribromoacridone (2·0 g.) and phosphorus oxychloride (5 ml.) were refluxed (90 min.) and the product poured into ice (100 g.), ammonia (100 ml.; *d* 0·880), and chloroform (125 ml.). The chloroform layer was boiled to dissolve all the solid; on cooling to 0°, 1 : 3 : 7-tribromo-5-chloroacridine crystallised (1·15 g.). It separated from benzene in pale yellow needles, m. p. 232—233° (Found: C, 35·0; H, 1·2%). 1 : 3 : 7-Tribromo-5-(4-dimethylaminophenyl)acridine (method 3) separated from benzene as yellow needles which change to red at about 200°, or occasionally as scarlet prisms; both forms have

m. p. 292—293°. 1 : 3 : 7-Tribromo-5-*p*-diethylaminophenylacridine, similarly prepared and purified, had m. p. 260° (Found: C, 49·5; H, 3·4%).

2′ : 4′-*Dibromobenzanilide*.—Benzanilide (49 g.), anhydrous sodium acetate (45 g.), bromine (26 ml.), and glacial acetic acid (300 ml.) were heated on a steam-bath for 18 hours and allowed to cool (cf. Chattaway and Clemo, *J.*, 1916, **109**, 91). The precipitate was collected and after being washed with a little acetic acid and much water crystallised from ethanol, to give 2′ : 4′-dibromobenzanilide as colourless needles, m. p. 138° (67 g.) (Wittig *et al.*, *Annalen*, 1929, **469**, 11, give m. p. 139°).

N-(2 : 4-*Dibromophenyl*)*benzimidoyl Chloride*.—2′ : 4′-Dibromobenzanilide (35·5 g.) and powdered phosphorus pentachloride (22·8 g.) were heated on a steam-bath for 30 minutes. The phosphorus oxychloride was removed as for (XIV), and the residue on crystallisation from light petroleum (b. p. 60—80°; sodium-dried) gave *N*-(2 : 4-*dibromophenyl*)*benzimidoyl chloride* as needles, m. p. 95·5° (31 g.) (Found: C, 41·8; H, 2·4. $C_{13}H_8NClBr_2$ requires C, 41·8; H, 2·2%).

1 : 3 : 7 : 9-*Tetrabromoacridone*.—A solution of the above chloride (13·2 g.) in dry ether (100 ml.) was added with shaking to a mixture of methyl 3 : 5-dibromosalicylate (10·9 g.) and a solution of sodium (0·8 g.) in dry ethanol (100 ml.). Next day the solvent was removed *in vacuo*, and after addition of water the semi-solid 4 : 6-dibromo-2-carbomethoxyphenyl *N*-(2 : 4-dibromophenyl)benzimidate was collected. Attempts to crystallise this material failed. The imidate (5 g.) was heated at 260° for 5 minutes to effect rearrangement to methyl *N*-benzoyl-4 : 6 : 2′ : 4′-tetrabromodiphenylamine-2-carboxylate, also obtained only as a glass. This (4·0 g.) was heated at 200° for 1 min. with concentrated sulphuric acid (10 ml.; *d* 1·84), and, on cooling, 1 : 3 : 7 : 9-tetrabromoacridone separated in minute pale yellow needles which were washed with sulphuric acid, acetic acid, and ethanol (yield, 2·1 g.). After crystallisation from *m*-cresol–acetic acid the acridone had m. p. 308—309° (Found: C, 30·6; H, 1·1%).

1 : 3 : 7 : 9-*Tetrabromo*-5-*chloroacridine*.—This was prepared from the acridone as before and separated from benzene as pale yellow needles changing to yellow prisms, m. p. 254° (Found: C, 29·9; H, 0·8%). 1 : 3 : 7 : 9-Tetrabromo-5-*p*-dimethylaminophenylacridine (method 3) separated from benzene–ethanol in scarlet needles, m. p. 308—309° (Found: C, 41·4; H, 2·4%). 1 : 3 : 7 : 9-Tetrabromo-5-*p*-diethylaminophenylacridine (method 3) separated from benzene as orange-red needles, m. p. 268—269°.

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48. *The Photochemical Addition of Benzaldehyde to Quinones.*

By R. F. MOORE and WILLIAM A. WATERS.

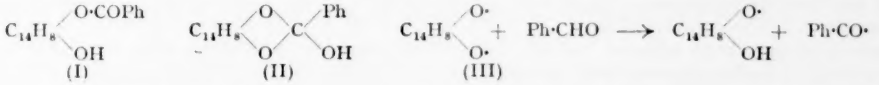
Chemical and spectroscopic evidence indicates that the photochemical addition product of benzaldehyde and phenanthraquinone has the formula (I) originally proposed by Klinger (*Annalen*, 1888, **249**, 143) and not the cyclic structure (II) suggested by Schönberg and Moubasher (*J.*, 1939, 1430). An analogue of (I) has been prepared from benzaldehyde and chloranil. A chain mechanism for the photochemical addition is proposed.

IN connection with recent studies of the addition of free radicals to the oxygen atoms of quinones (Bickel and Waters, *J.*, 1950, 1764; Moore and Waters, *J.*, 1952, 2432) we have reinvestigated the photochemical addition of benzaldehyde to phenanthraquinone, first reported by Klinger (*loc. cit.*) and later studied by Schönberg and Moubasher (*loc. cit.*), Mustapha (*J.*, 1949, S 83), and Schönberg, Latif, Moubasher, and Sina (*J.*, 1951, 1354). Klinger, who exposed his mixture to sunlight in Germany for a few days, obtained a colourless crystalline product, m. p. 177—178°, to which, from the results of ultimate analysis and alkaline hydrolysis to benzoic acid, he assigned the constitution 9-benzoyloxy-10-hydroxyphenanthrene (I). Schönberg and Moubasher, who obtained a product of the same m. p. after exposing their mixture for several days to sunlight in Cairo, put forward the alternative cyclic formula (II) since (*a*) the product does not give a ferric chloride reaction and (*b*) from a similar reaction, using *p*-chlorobenzaldehyde, they obtained an analogous product which after methylation with diazomethane was hydrolysed by alkali

to give methyl *p*-chlorobenzoate. In 1951 Schönberg and his colleagues suggested that the two forms might exhibit ring–chain tautomerism in solution.

We have now found that an identical substance can be prepared in nearly theoretical yield by shaking for 3 days, under nitrogen, a solution of phenanthraquinone in benzaldehyde in a thin-walled glass bulb exposed to the radiation from a 300-watt Hanovia ultra-violet lamp. All these reported yields are so high that a photochemical chain reaction of very long chain-length must be involved.

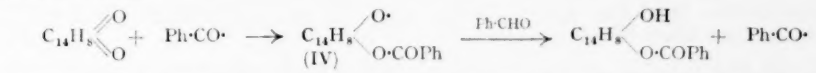
By the kindness of Professor A. Schönberg we have been able to compare our product with his. The two specimens have identical m. p.s and mixed m. p., and their infra-red spectra are completely identical between 5000 and 660 cm.$^{-1}$. The infra-red spectrum accords with formula (I), since it shows a pronounced absorption maximum at 5·82 μ corresponding to the stretching frequency of a C=O group in a benzoate ester. Other spectral features expected for structure (I) are exhibited. Since the infra-red spectra were measured by using pastes of the solid materials in a liquid-paraffin base there is little chance of conversion from (I) into (II).



We have also methylated our product with diazomethane exactly as described by Schönberg and Moubasher and obtained a crystalline methyl ether, m. p. 134° (they give 80°), which on hydrolysis yielded benzoic acid and 9-hydroxy-10-methoxyphenanthrene. The latter on acetylation gave a stable acetoxy-derivative identical with that prepared by methylating 9-acetoxy-10-hydroxyphenanthrene.

Our photochemical addition product (I), when finely dispersed by precipitation with water from alcoholic solution, promptly dissolved in cold aqueous sodium hydroxide. It did not give a ferric chloride colour, but this is not a diagnostic test for a completely *ortho*- and *para*-blocked phenol. A similar sequence of reactions has been carried out with the photochemical addition product of anisaldehyde and phenanthraquinone (Klinger, *Annalen*, 1911, **382**, 218). Moreover, we have found that chloranil and benzaldehyde combine photochemically in a very similar way to give the monobenzoate of tetrachloroquinol: no ring closure is possible here.

We suggest, from the relation of this to our earlier work (*loc. cit.*), that the process has the following radical-chain mechanism: (i) Photochemical activation of the quinone to a di-radical (III). (ii) Hydrogen abstraction by (III) from benzaldehyde (chain-starting). (iii) A long chain reaction in which benzoyl radicals add on to unactivated phenanthraquinone molecules, giving aryloxy-radicals (IV) which can dehydrogenate fresh benzaldehyde molecules:



With unsymmetrical quinones, or quinoneimines, this chain would take a unidirectional course, the radical (IV) of greater stability being formed (compare Schönberg and Awad, *J.*, 1945, 197).

Experimental

Irradiation of Phenanthraquinone with Benzaldehyde.—The quinone (5 g.) and dry benzaldehyde (15 g.), sealed under nitrogen in a thin-walled bulb of soda-glass, were shaken for 75 hours in the radiation from a 300-w. Hanovia ultra-violet lamp. The quinone dissolved, giving a dark orange solution from which a white solid separated. After removal of excess of benzaldehyde under reduced pressure, this residue (6·5 g.) was washed with, and crystallised from benzene, forming colourless woolly needles, m. p. 185° (some decomp.) (Found: C, 80·1; H, 4·7. Calc. for $C_{21}H_{14}O_3$: C, 80·3; H, 4·4%), which had the properties described above. The infra-red spectrum of a dispersion of the solid in paraffin paste exhibited the following characteristic bands: 2·99 μ, H–O stretching; 5·82 μ, C=O stretching in benzoate ester; 7·8—8·0 μ, –O–CO– stretching; 13·32 μ, bending frequencies of C_6H_4 in phenanthrene rings;

13·85 and 14·16 μ, bending frequencies of C_6H_5. A sample of the solid, thought to have structure (II), sent to us by Prof. A. Schönberg had an identical m. p. and mixed m. p. and a completely coincident infra-red spectrum.

Benzoylation of our material gave 9 : 10-dibenzoyloxyphenanthrene, m. p. 218° unchanged in admixture with an authentic specimen.

Methylation of our Photochemical Product (cf. Schönberg and Moubasher, *loc. cit.*).—To ethereal diazomethane (from 4·5 g. of methylnitrosourea) at 0°, 3 g. of the substance were added gradually, and the solution was stored at 0° for 24 hours. The product (2·8 g.) formed colourless prisms (from ethanol), m. p. 134° (Found : C, 80·3; H, 5·2. $C_{22}H_{16}O_3$ requires C, 80·5; H, 4·9%), evidently of 9-*benzoyloxy*-10-*methoxyphenanthrene*, having an infra-red spectrum with strong absorption bands at: 5·74 μ, due to C=O stretching; grouped bands at 7·9—8·15 μ, due to C–O–C stretching; 13·30 μ, due to C_6H_4; 13·79 and 14·15 μ, due to C_6H_5.

The methyl ether (1 g.) was refluxed for 15 minutes with potassium hydroxide (3 g.) in water–ethanol (10 ml., 20 ml.). The dried chloroform extract of the acidified solution on evaporation gave an oil which was obtained as colourless needles (from light petroleum), m. p. 95—102°, after some difficulty (Goldschmidt and Schmidt, *Ber.*, 1922, **55**, 320, give m. p. 103° for 9-hydroxy-10-methoxyphenanthrene). These were acetylated by warming them for 2½ hours with acetic anhydride. The product (Found : C, 76·5, H, 5·4. $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·2%) formed prisms (from ethanol), m. p. 113° unchanged after admixture with a specimen of 9-*acetoxy*-10-*methoxyphenanthrene*, prepared by methylating the hydroxy-phenanthrene (*idem*, *ibid.*, give m. p. 170°, decomp.)

Irradiation of Phenanthraquinone and Anisaldehyde (cf. Klinger, 1911, *loc. cit.*).—Phenanthraquinone (3 g.) and anisaldehyde (9 g.) in benzene (20 ml.) were irradiated, as described above, for 70 hours. The white solid formed woolly needles (4·8 g., 100%), m. p. 231° (decomp.), from acetic acid (Found : C, 77·0; H, 4·9. Calc. for $C_{22}H_{16}O_4$: C, 76·8; H, 4·6%). This 9-anisoyloxy-10-hydroxyphenanthrene gives no colour with ferric chloride, and can be dissolved in cold sodium hydroxide only if finely divided by precipitation with water from alcohol or acetone solution. For methylation the solid (3 g.), which was very sparingly soluble in ether, was dissolved in dry dioxan–ether and added to ethereal diazomethane at 0°. The 9-*anisoyloxy*-10-*methoxyphenanthrene* (2 g.) crystallised from ethanol in needles, m. p. 158° (Found : C, 76·7; H, 5·2. $C_{23}H_{18}O_4$ requires C, 77·1; H, 5·0%). Attempted hydrolysis of this substance by shaking it with 20% sodium hydroxide at 40° for ½ hour failed (cf. Schönberg and Moubasher, *loc. cit.*). Hydrolysis by alcoholic alkali, followed by acetylation, yielded *p*-anisic acid, m. p. 184°, and 9-acetoxy-10-methoxyphenanthrene, m. p. and mixed m. p. 113°.

Irradiation of Chloranil and Benzaldehyde.—Chloranil (2 g.) in benzaldehyde (10 ml.) was irradiated by a 500-w. Hanovia ultra-violet lamp for 96 hours, the excess of benzaldehyde removed under reduced pressure, and the residual gum rubbed with acetic acid until it solidified. Crystallisation from this solvent gave the *monobenzoate* of tetrachloroquinol as colourless prisms (1 g.), m. p. 180° (Found : C, 44·8; H, 1·9; Cl, 40·7. $C_{13}H_6O_3Cl_4$ requires C, 44·4; H, 1·7; Cl, 40·3%), which gave no ferric chloride colour but dissolved in cold dilute sodium hydroxide solution. Benzoylation with benzoyl chloride in boiling pyridine solution gave the dibenzoate, colourless prisms (from glacial acetic acid), m. p. 238° not depressed on admixture with a specimen prepared from tetrachloroquinol.

We thank Professor A. Schönberg for allowing us to carry out the direct comparison of our respective products, and also Dr. F. B. Strauss for help in the measurement and interpretation of the infra-red spectra. The micro-analyses were made by Drs. Weiler and Strauss.

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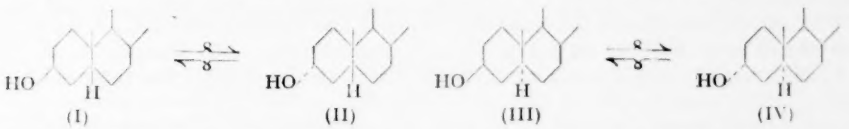
49. *Steroids and Walden Inversion. Part IX.* Epimerisation at* $C_{(17)}$.

By J. Elks and C. W. Shoppee.

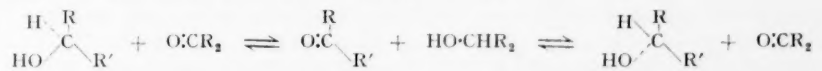
Androstan-17α-ol, prepared from androstan-17β-yl toluene-*p*-sulphonate by acetolysis and hydrolysis, and androstan-17β-ol failed to undergo interconversion on treatment with sodium ethoxide at 180° in the presence of a ketone to act as hydrogen-acceptor.

Epimerisation of a 3-hydroxy-steroid was first observed by Dorée and Gardner (*J.*, 1908, 1630) who found that coprostanol (I) was converted into *epi*coprostanol (II) when heated with sodium–amyl alcohol. Interconversion of epimeric 3-hydroxy-steroids was first demonstrated by Windaus and Uibrig (*Ber.*, 1914, **47**, 2384; 1915, **48**, 857; 1916, **49**, 1724) who showed that cholestanol (III) and *epi*cholestanol (IV) by treatment with sodium ethoxide at 180° furnished an equilibrium mixture containing ~90% of the former, whilst coprostanol (I) and *epi*coprostanol (II) gave an equilibrium mixture containing ~90% of the latter.



Subsequently, Marker, Kamm, Wittle, Oakwood, Lawson and Laucius (*J. Amer. Chem. Soc.*, 1937, **59**, 2291) converted pregnane-3β : 20β-diol (as I) into pregnane-3α : 20β-diol (as II) and prepared *allo*pregnane-3β : 20α-diol (as III) from *allo*pregnane-3α : 20α-diol (as IV) by treatment with sodium–xylene. It appears that here the steroid alcohol furnishes steroid alkoxide for its own interconversion, since Barnett, Heilbron, Jones, and Verrill (*J.*, 1940, 1390) were able to epimerise cholesterol, cholestanol, lumisterol, and *neo*ergosterol by use of aluminium *iso*propoxide–xylene. Beynon, Heilbron, and Spring (*J.*, 1937, 406) similarly observed almost complete epimerisation of *epi*cholestanol (IV) to cholestanol (III) in the presence of potassium in boiling benzene.

The mechanism of epimerisation has been shown to involve an oxidation–reduction process, analogous to that operating in Oppenauer oxidation and Meerwein–Ponndorf reduction, by the elegant experiments of Aschner and Doering (*J. Amer. Chem. Soc.*, 1949, **71**, 838; cf. Hückel and Naab, *Ber.*, 1931, **64**, 2137); these authors showed that optically active secondary alcohols are not racemised by alkoxides unless a trace of a ketone can arise, or is added, to permit establishment of the equilibrium :



The position of equilibrium in the epimerisations (I ⇌ II) and (III ⇌ IV) is now recognised to result from the greater steric compression to which atoms or groups possessing the polar conformation are subjected compared with the same atoms or groups possessing the corresponding equatorial conformation † (Shoppee, *Chem. and Ind.*, 1952, **86**; cf. Barton, *Experientia*, 1950, **6**, 316). Such steric compressions have been observed to control the thermodynamic stabilities of steroid hydroxy-compounds epimeric at $C_{(4)}$ (Barton and Rosenfelder, *J.*, 1951, 1048), $C_{(6)}$ (Shoppee and Summers, *J.*, 1952, 3361), $C_{(7)}$ (Barton, *loc. cit.*; cf. Heilbron, Shaw, and Spring, *Rec. Trav. chim.*, 1938, **57**, 529; Cremlyn and Shoppee, unpublished observation), $C_{(11)}$ (Gallagher *et al.*, *J. Biol. Chem.*, 1946, **162**, 511, 521, 533;

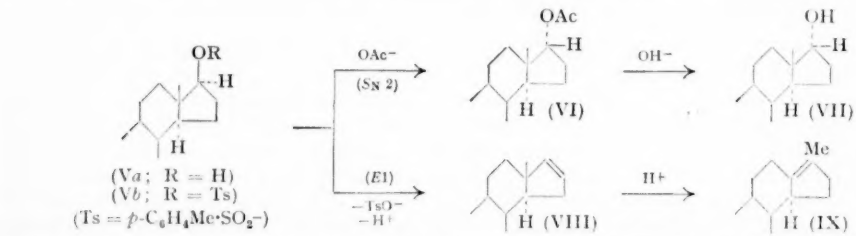
* Part VIII, *J.*, 3374.

† Because ring A in cholesterol is a chair form, it is consistent that the equilibrium cholesterol (90%) ⇌ *epi*cholesterol (10%) (Heilbron *et al.*, *loc. cit.*) favours the former compound (3β-OH : equatorial). In the case of the equilibrium lumisterol (60%) ⇌ *epi*lumisterol (40%) it is to be noted that, despite *cis*-union of rings A and B, ring A is a chair form but the 3β-hydroxyl group here possesses the polar conformation, whilst in the case of lumistanol (3β-OH : polar) sodium methoxide at 200° yields *epi*lumistanol (3α-OH : equatorial) (Ahrens, Fernholz, and Stoll, *Annalen*, 1933, **500**, 109).

Fieser, *Experientia*, 1950, **6**, 312), and $C_{(12)}$ (Gallagher *et al.*, *J. Biol. Chem.*, 1946, **162**, 539; Gallagher and Borgstrom, *ibid.*, 1946, **164**, 791). It seemed therefore of interest to examine the situation at $C_{(17)}$.

Both reaction rates and equilibria at $C_{(17)}$ are strongly influenced by steric compression. The situation has been discussed by Gallagher and Kritchevsky (*J. Amer. Chem. Soc.*, 1950, **72**, 882), Fieser (*loc. cit.*), and by Shoppee (*Nature*, 1950, **166**, 107) who suggested that asymmetric induction may be operative in addition to steric compression. The products of reactions at $C_{(17)}$ in C/D-*trans*-steroids consist largely of the epimerides in which the original 17-substituent takes up the β-configuration which, as Barton (*loc. cit.*) has pointed out, may be regarded as possessing the equatorial conformation. Thus epimerisation of (*a*) 17-acyl or (*b*) 17-carbalkoxy-steroids by acid or alkaline reagents furnishes mixtures in which the 17β-form predominates [(*a*) Butenandt *et al.*, *Ber.*, 1935, **68**, 1847; 1937, **70**, 96; 1939, **72**, 1112; Shoppee, *J.*, 1949, 1671; (*b*) Shoppee, *Helv. Chim. Acta*, 1940, **23**, 925; von Euw and Reichstein, *ibid.*, 1944, **27**, 1851; Sorkin and Reichstein, *ibid.*, 1946, **29**, 1218; Heusser, Meier, and Ruzicka, *ibid.*, p. 1250]. It might therefore be expected that a 17α-hydroxy-steroid would undergo almost complete transformation into the 17β-hydroxy-epimeride.

The compounds chosen for examination were the androstan-17-ols. A quantity of androstan-17β-ol (V*a*) was most kindly made available by Dr. G. Rosenkranz of Syntex Ltd., Mexico City, and a small quantity of androstan-17α-ol (VII) was prepared from it.



After treatment of androstan-17β-ol (V*a*) with toluene-*p*-sulphonyl chloride in pyridine at 20°, the alcohol was recovered unchanged, but prolonged reaction at 45—50° gave (V*b*) in satisfactory yield. Plattner and Fürst (*Helv. Chim. Acta*, 1943, **26**, 2266), and Prelog and Szpilfogel (*ibid.*, 1944, **27**, 390), have shown that acetolysis of 3-toluene-*p*-sulphonyloxy-steroids (saturated at $C_{(5)}$) occurs with inversion of configuration at $C_{(3)}$; the replacement described by Plattner and Fürst is accompanied by elimination, a considerable quantity of the Δ^2- or Δ^3-olefin being formed. Treatment of (V*b*) with potassium acetate in glacial acetic acid gave rise to much unsaturated material and no pure compound with the properties of the acetate (VI) could be isolated. In subsequent experiments, the crude acetolysis product was hydrolysed with alcoholic potassium hydroxide and the resulting mixture subjected to chromatography. From the more strongly absorbed fractions a small amount (~5% yield) of androstan-17α-ol (VII) was isolated together with a little of the starting material (V*b*). That the chief reaction was elimination rather than replacement of the toluene-*p*-sulphonyloxy-group was indicated by the fact that the greater part of the reaction product was rapidly eluted from the column by pentane and gave a yellow colour with tetranitromethane–chloroform. This material could not be caused to crystallise and, although androst-16-ene (VIII), which exists in two forms, m. p. 44°, $[\alpha]_D$ +18° (Kägi and Miescher, *ibid.*, 1939, **22**, 683), and m. p. 74·5—75·5°, $[\alpha]_D$ +17° (Prelog, Ruzicka, and Wieland, *ibid.*, 1944, **27**, 66), may have been present, it seems probable that the main constituent was *ψ*-androstene (IX), an oil which is produced by treatment of (VIII) with acidic reagents (Miescher and Kägi, *ibid.*, 1949, **32**, 761); the colour test described by Miescher and Kägi for *ψ*-androstene was positive.

Reduction of androstan-17-one with lithium aluminium hydride gives almost exclusively androstan-17β-ol, but it has been found possible chromatographically to isolate small quantities (*ca.* 0·25%) of androstan-17α-ol. A gift of androstan-17α-ol (200 mg.) by

Dr. K. Miescher of CIBA, Basle, supplemented the small quantities available by the above method, and enabled the investigation to be completed.

It was found that a synthetic mixture of androstan-17α-ol and androstan-17β-ol could be separated quite satisfactorily by chromatography (see above), the 17α-ol being eluted with a mixture of equal volumes of pentane and benzene and the 17β-ol with pure benzene. The intermediate mixed fraction amounted to less than 10%.

The epimerisation reactions were carried out with alcoholic sodium methoxide at 180° (Windaus, *Ber.*, **1916**, **49**, 1724). After such treatment of androstan-17β-ol for 16 hours, some 90% of it was recovered by chromatography. Moreover, there was no evidence of the presence in the more readily eluted fractions of the 17α-ol as judged by the Kägi–Miescher colour reaction (*Helv. Chim. Acta*, 1939, **22**, 683). Since this result might indicate that under the conditions of reaction there was an equilibrium which was very much in favour of the 17β-epimeride (as indeed analogy suggests), androstan-17α-ol was subjected to similar treatment. Here again some 90% was recovered and no trace could be found of the 17β-epimeride. These experiments were repeated with the addition of a small quantity of androstan-17-one with precisely similar results. It seems that under the conditions which cause interconversion of the epimeric forms of 3-hydroxy-steroids, 17-hydroxy-groups (like 20-hydroxy-groups in the side-chain) are unaffected.

Experimental

M. p.s were determined thermo-electrically on a Kofler block; limit of error ±2°. Solvents for chromatographic operations were rigorously purified and dried and, unless stated otherwise, aluminium oxide (Spence type H, activity II) was used. For drying of ethereal extracts, brief treatment with anhydrous sodium sulphate was used. Microanalyses are by Drs. Weiler and Strauss, Oxford.

*Androstan-17β-yl Toluene-*p*-sulphonate* (V*b*).—Androstan-17β-ol (1·0 g.) was dried by repeated evaporation with benzene at 10 mm. and by heating at 100°/0·01 mm. for 30 minutes. It was dissolved in specially dried pyridine (20 c.c.), purified toluene-*p*-sulphonyl chloride (3·0 g.) added, and the mixture kept at 45—50° for 4 days. The cold solution was treated with water (5 c.c.) whereupon an oil separated which rapidly crystallised in needles. After some hours the crystals were washed with N-hydrochloric acid and with water and dried (m. p. 133—138°). Recrystallisation from acetone gave needles, m. p. 138—139° (1·03 g.); a second crop obtained from the mother-liquors weighed 0·17 g. Again recrystallised from acetone *androstan-17β-yl toluene-*p*-sulphonate* had m. p. 139—140°, $[\alpha]_D$ 0° ± 2° (*c* = 1·00 in $CHCl_3$) (Found, after drying at 20°/0·01 mm.: C, 72·7; H, 8·8. $C_{26}H_{38}O_3S$ requires C, 72·5; H, 8·9%).

Acetolysis. The toluene-*p*-sulphonate (V*b*) (200 mg.), anhydrous potassium acetate (200 mg.), and acetic acid (4 c.c.) were refluxed for 3 hours. The cold solution was diluted with water and the resultant oil extracted with ether. The extract was washed with 2N-sodium carbonate solution, then with water, dried, and evaporated. The residue was refluxed for 2 hours with a solution of potassium hydroxide (0·3 g.) in water (0·3 c.c.) and ethanol (3 c.c.); ethanol was removed in a vacuum, the residue diluted with water, and the product repeatedly extracted with ether. The extract was washed successively with 2N-hydrochloric acid, sodium carbonate solution, and water, dried, and evaporated. The residual yellow oil (129 mg.) was dried by repeated azeotropic distillation with benzene and chromatographed in pentane on aluminium oxide (4 g.) prepared in pentane; 15-c.c. batches of each eluant were used. The column was eluted with pentane (Fr. 1—5), pentane–benzene (1 : 1) (Fr. 6—15), benzene (Fr. 16—20), and ether (Fr. 21—25). Fractions 1—3 (90·4 mg.) were combined but the oil did not crystallise. A small portion was dissolved in acetic acid, and one drop of concentrated sulphuric acid added; addition of a dilute solution of bromine in acetic acid gave an intense blue colour characteristic of ψ-androstene (Miescher and Kägi, *loc. cit.*). Fractions 6—11 crystallised partly when kept; they were combined and crystallised from aqueous acetone, to give androstan-17β-yl toluene-*p*-sulphonate, m. p. 133—137°, mixed m. p. 134—139°. Fractions 16—20 contained insignificant traces of oil. Fractions 21—24 were crystalline and were combined and recrystallised from methanol, to give androstan-17α-ol, double m. p. 139° with transformation to needles, m. p. 147° (5 mg.); a second crystallisation from methanol gave small needles, m. p. 146·5—147·5°, not depressed by admixture with a genuine specimen, m. p. 148—151°. The colour test for androstan-17α-ol described by Miescher and Kägi was positive, whilst by admixture with androstan-17β-ol the m. p. was depressed to *ca.* 120°.

Chromatographic Separation of Androstan-17α-ol and Androstan-17β-ol.—A synthetic mixture of androstan-17α-ol (28 mg.) and androstan-17β-ol (25 mg.) was chromatographed in pentane–benzene (1 : 5; 6 c.c.) on aluminium oxide (2 g.) prepared in pentane (5-c.c. eluant batches). Fractions 1—20 obtained by elution with pentane–benzene (1 : 1) gave androstan-17α-ol (18·8 mg.), m. p. 152—153° after crystallisation from methanol. Further elution (Fr. 21—24) and with benzene (Fr. 25) gave mixtures, m. p. 130—155°, of the epimerides (4·7 mg.). Fractions 26—29 obtained with benzene, fractions 30—32 with benzene–ether (1 : 1), and fractions 22—35 with ether gave androstan-17β-ol (21·2 mg.), m. p. 168—169° after recrystallisation from benzene–pentane.

Reduction of Androstan-17-one with Lithium Aluminium Hydride [By M. FINKELSTEIN].—Androstan-17-one (m. p. 118—119°; 791 mg.) was treated with lithium aluminium hydride (500 mg.) in ether. The reaction mixture was worked up in the usual way and the product (780 mg.) chromatographed on a column of aluminium oxide (20 g.) prepared in pentane; 100 c.c. of solvent were used for each elution. The column was eluted successively with pentane, pentane–benzene (1 : 1), benzene, and benzene–ether mixtures (1 : 19, 1 : 7 twice), and finally twice with ether, giving fractions 1—8. Fraction 2 was an oil [11 mg.; (—)] (+, – refer to response to the Kägi–Miescher test); fraction 3 was semicrystalline [2 mg.; weak (+)]. Fraction 4 had m. p. 129—157° [8 mg.; (+)]; fractions 5 and 6 had m. p. 132—147° [20 mg.; (+)] and m. p. 169° [284 mg.; (–)] respectively. Fractions 7 and 8 had m. p. 169° [449 mg.; (–)]. Fractions 2—5 were united (22 mg.) and rechromatographed on aluminium oxide (1 g.) in pentane (3-c.c. eluant batches). Elution with pentane–benzene (1 : 1) gave oil [3 mg.; (–)]; use of benzene gave material, m. p. 99—103° [1 mg.; (–)]. Further elution with benzene and with benzene–ether (1 : 19) gave fractions 4′ and 5′, each showing a double m. p. 137—139° and 150—152° [1 mg.; 1 mg.; (+), (+)]; further elution with benzene–ether (1 : 19) gave fractions 6′ and 7′, m. p. 157—160° and 165—168° [5 mg.; 4 mg.; (–); (–)]. Elution with benzene–ether (1 : 9) (Fr. 8′) gave material, m. p. 166—168° (4·5 mg.; (–)]. Fractions 3′ and 4′ consisted of androstan-17α-ol, which showed the characteristic double m. p. 137—139° with transformation to needles, m. p. 152°, unchanged by admixture with a genuine specimen. Fractions 6′, 7′, and 8′ consisted of androstan-17β-ol.

Equilibration Experiments.—(*a*) Androstan-17β-ol (m. p. 168°; 100 mg.) was heated with a solution of sodium (0·4 g.) in dry ethanol (10 c.c.) in a sealed tube at 180° for 15 hr. The product was chromatographed in pentane–benzene (1 : 1), on aluminium oxide (4 g.) prepared in pentane (10-c.c. eluant batches). Elution with benzene–pentane (1 : 1) (Fr. 1—7) and with benzene (Fr. 8, 9) furnished no crystalline material. Further elution with benzene gave crystals, m. p. 101—115°, and a series of products (Fr. 11—22) having m. p. 132—140° rising to 159—162°. Use of benzene–ether (1 : 4) (Fr. 23—34) gave material, m. p. 162—167°. A single elution with ether gave a trace of material, m. p. 152—158°. Fractions 18—35 (86·1 mg.) were combined and crystallised from benzene–pentane to give androstan-17β-ol (65·8 mg.), m. p. 166—167°, undepressed by admixture with a genuine specimen. Fractions 9—17 were united (8 mg.) and melted between 132° and 156°; the absence of androstan-17α-ol was shown by a negative Kägi–Miescher test, and crystallisation from pentane gave androstan-17β-ol (3·7 mg.), m. p. 166—167°. No further crystalline material could be obtained from the mother-liquor.

(*b*) Androstan-17α-ol (m. p. 148—151°; 25 mg.) was heated with a solution of sodium (0·1 g.) in dry ethanol (2·5 c.c.) in a sealed tube at 180° for 15 hr. The product (25 mg.) melted at 140—146° after softening from 130° and gave a strongly positive Kägi–Miescher test; it was chromatographed on aluminium oxide (1 g.) prepared in pentane (5-c.c. eluant batches). Elution with pentane and with benzene–pentane (1 : 1) (Fr. 6) furnished no material; further elution with benzene–pentane (1 : 1) (Fr. 7—19) gave crystalline material, m. p. 146—148°. Use of benzene (Fr. 20—24) gave crystals, m. p. 146—147°, 147—148°, 146—148°, 144—147°, and 144—146°. Further elution with benzene and benzene–ether (1 : 1) furnished only traces of material, whilst elution with ether furnished no material. Fractions 7—25 were united (22·6 mg.) and crystallised from methanol, to give androstan-17α-ol (13·2 mg.), m. p. 148—149°; a second crop (5·8 mg.) obtained by concentration of the mother-liquors had m. p. 144—148°. These products mixed with androstan-17α-ol gave no depression, but by admixture with androstan-17β-ol melted from 124° upwards.

(*c*) [By G. H. R. SUMMERS.] Androstan-17α-ol (m. p. 148—151°; 73 mg.) was heated with a solution of sodium in *tert.*-butanol (5 c.c., prepared from 0·25 g. of sodium and 45 c.c. of *tert.*-butanol) in the presence of androstan-17-one (m. p. 118—119°; 18 mg.) in a sealed tube at 180° for 48 hr. The product, a white crystalline solid, was chromatographed on aluminium oxide (3 g.) in pentane (20-c.c. eluant batches). Elution with pentane gave androstan-17-one (16·8

mg.), m. p. and mixed m. p. 118°; elution with pentane–benzene (2 : 1, 1 : 1, and 1 : 3) gave androstan-17α-ol (57 mg.), m. p. 148—152° undepressed by admixture with a genuine specimen. Elution with benzene and benzene–ether (1 : 1) gave crystalline material (20·8 mg.) which was rechromatographed on aluminium oxide (1 g.) in benzene–pentane (1 : 1) (eluant batches of 20 c.c.). Fractions 1—7 obtained with benzene–pentane (1 : 1) had the following m. p.s: 149—153°, 150—152°, 149—151°, 150—151°, 151°, 150°, and 146—153°, in each case after transition to needles at *ca.* 138°, and all gave a positive Kägi–Miescher test; fraction 8 obtained with benzene contained only a trace of material, but fraction 9 obtained with benzene–ether (3 : 2) gave material of m. p. 138° with transition to needles, m. p. 150°, giving a positive Kägi–Miescher test; elution with ether gave no material. The total solid recovered amounted to 17 mg. and consisted of androstan-17α-ol, no trace of androstan-17β-ol being detected.

One of us (J. E.) thanks Glaxo Laboratories Ltd. for the opportunity to participate in this work. We gratefully acknowledge gifts of androstan-17-one and androstan-17β-ol from Dr. G. Rosenkranz of Syntex Ltd., Mexico City, androstan-17α-ol from Dr. K. Miescher of CIBA, Basle, and a grant from the Royal Society which has partly defrayed the cost of this work.

UNIVERSITY COLLEGE, SWANSEA, UNIVERSITY OF WALES. [*Received September 9th*, 1952.

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50. *Potential Carcinogens. Part I.* Δ^6-*Steroids.*

By D. L. GARMAISE and C. W. SHOPPEE.

Partial synthesis of some Δ^6-steroids analogous in structure to the sex hormones has been accomplished, *viz.*, 17β-acetoxyandrost-6-en-3-one and androst-6-ene-3 : 17-dione, which may be compared with testosterone acetate and androst-4-ene-3 : 17-dione respectively, and androst-6-ene-3β : 17β-diol.

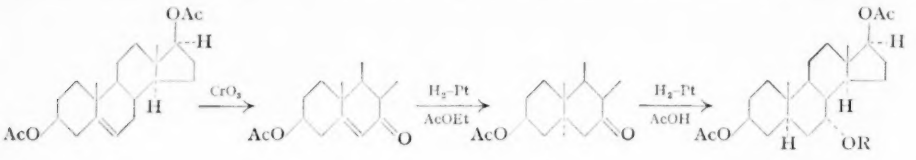
RECENT attempts to establish a connection between electron-density distribution, chemical reactivity, and carcinogenicity in unsaturated hydrocarbons (Pullman, *Compt. rend.*, 1945, **221**, 140; 1946, **222**, 392, 1501; Daudel, *ibid.*, 1946, **222**, 797; Badger, *J.*, 1949, 456; Cook and Schoental, *J.*, 1948, 170; 1950, 47) have focused attention on the phenanthrene 9 : 10-positions, termed the "K" region; the situation has been discussed by Sir Robert Robinson (*Brit. Med. J.*, 1946, **943**), by Haddow (*Brit. Med. Bull.*, 1947, **4**, 331) and, more recently, reviewed by Cook (*J.*, 1950, 1210). Since the chemical reactivity shown by the 9 : 10-positions in phenanthrene is ethylenic in character (cf. Hunsberger, Ketcham, and Gutowsky, *J. Amer. Chem. Soc.*, 1952, **74**, 4839), it seemed of interest to examine the growth-inhibitory properties of steroids containing an ethylenic linkage at the Δ^6-position. There appears to be a qualitative relation between growth inhibition and carcinogenic activity (Haddow, Harris, and Kon, *Biochem. J.*, 1945, **39**, ii), and the steroids selected were analogous to the sex hormones some of which are known to be implicated in some way in the changes leading to neoplasia.

An isolated Δ^6-linkage was first introduced into the steroid nucleus by pyrolysis of 3-acetoxycholestan-7α-yl benzoate (Barton and Rosenfelder, *J.*, 1949, 2459; Wintersteiner and Moore, *J. Amer. Chem. Soc.*, 1950, **72**, 1923; cf. Plattner, Heusser, Troxler, and Segré, *Helv. Chim. Acta*, 1948, **31**, 852); since homogeneous, mechanistically unimolecular, thermal elimination reactions require *cis*-geometry of the four centres involved [6α-H (equatorial)/7α-OBz (polar)] (Barton, *J.*, 1949, 2174; cf. Cristol and Hause, *J. Amer. Chem. Soc.*, 1952, **74**, 2193, and previous papers), the pyrolysis product was 3β-acetoxycholest-6-ene. The same compound was obtained by Barton and Rosenfelder (*loc. cit.*) by pyrolysis of 3β-acetoxycholestan-6β-yl benzoate [6β-OBz (polar)/7β-H (equatorial)]. Although the stereochemistry of the cholestane ring system forbids fulfilment of the requirement that the four centres must be coplanar to minimise the activation energy, with a probable adverse effect on yields, analogous routes to appropriate androst-6-enes were examined.

3β : 17β-Diacetoxyandrost-5-ene (I), prepared by reduction of dehydro*epi*androsterone with sodium–*n*-propanol and subsequent acetylation (Ruzicka and Wettstein, *Helv. Chim. Acta*, 1935, **18**, 1264), was oxidised by chromium trioxide to 3β : 17β-diacetoxyandrost-5-en-7-one (II) (Butenandt, Hausmann, and Paland, *Ber.*, 1938, **71**, 1316) which was hydrogenated

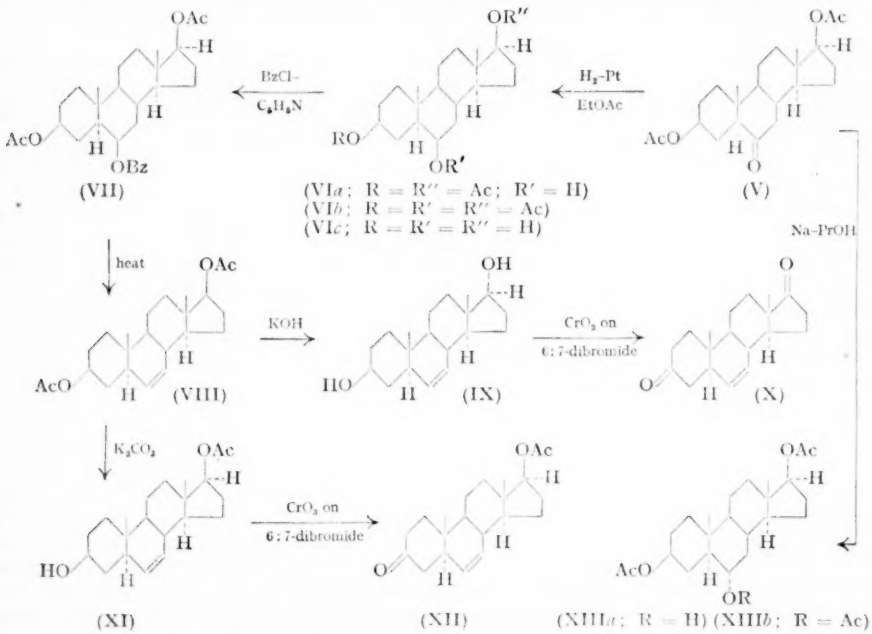
with platinum in ethyl acetate to 3β : 17β-diacetoxyandrostan-7-one (III), further hydrogenated with some difficulty on platinum in acetic acid to 3β : 17β-diacetoxyandrostan-7α-ol (IV*a*). The configuration at $C_{(7)}$ is supported by the molecular rotation difference $\Delta O = -74°$ since Barton and Klyne (*Chem. and Ind.*, 1948, 755) give $\Delta O\text{-}7\alpha = -59°$, $\Delta O\text{-}7\beta = +110°$; nevertheless a crystalline benzoate (IV*b*) could not be obtained and pyrolysis of the amorphous benzoate at 300—310°/0·05 mm. gave no crystalline product. The compounds (III) and (IV) are mentioned by Butenandt and Logemann in U.S.P. 2,170,124, but not described in detail.*

The alternative route to the androst-6-enes *via* the 6-substituted androstanes was more successful. 3β : 17β-Diacetoxyandrost-5-ene (I) was treated with sodium nitrite in nitric and acetic acids, to give the crude 6-nitro-derivative, which was reduced with zinc–acetic



(I) (II) (III) (IVa; R = H) (IVb; R = Bz)

acid to 3β : 17β-diacetoxyandrostan-6-one (V). The reduction of (V), which had to be carried out under conditions leading to a 6β-hydroxyl group without hydrolysis of the two acetoxyl groups, was accomplished by hydrogenation with platinum in ethyl acetate and



(VII) (VIa; R = R″ = Ac; R′ = H) (V)
(VIb; R = R′ = R″ = Ac)
(VIc; R = R′ = R″ = H)
(VIII) (IX) (X)
(XI) (XII) (XIIIa; R = H) (XIIIb; R = Ac)

yielded 3β : 17β-diacetoxyandrostan-6β-ol (VI*a*) [cf. reduction of cholestan-6-one to cholestan-6β-ol (Shoppee and Summers, *J.*, 1952, **3361**) and of 6-ketocholestan-3β-yl acetate to 6β-hydroxycholestan-3β-yl acetate (Barton and Rosenfelder, *loc. cit.*)]. Acetylation furnished 3β : 6β : 17β-triacetoxyandrostane (VI*b*), which by alkaline hydrolysis yielded

* Since this work was completed these compounds have been described by Heusler and Wettstein (*Helv. Chim. Acta*, 1952, **35**, 284).

androstane-3β : 6β : 17β-triol (VI*c*). Reduction of (V) with sodium and *n*-propanol produced, in accordance with expectation, the more thermodynamically stable 6-epimeride of (VI*c*; 6β-OH, polar), namely, androstane-3β : 6α : 17β-triol (XIII*a*; 6α-OH, equatorial), which by acetylation gave the triacetate (XIII*b*).

The configurations assigned are consistent with the molecular rotation differences found for these triols and their triacetates. Use, as reference compounds, of androstane-3β : 17β-diol, $[M]_D$ +23°, and 3β : 17β-diacetoxyandrostane, $[M]_D$ −8°, gives the molecular-rotation contributions of the 6-hydroxy- and 6-acetoxy-groups as follows:

	ΔO		ΔAc
Androstane-3β : 6β : 17β-triol	−48°	Triacetate	−105°
Androstane-3β : 6α : 17β-triol	+35°	Triacetate	+125°

Barton and Klyne (*loc. cit.*) give the following generalised values: ΔO-6β = −50°, ΔO-6α = +55°; ΔAc-6β = −110°, ΔAc-6α = +210°.

Benzoylation of (VI*a*) yielded 3β : 17β-diacetoxyandrostan-6β-yl benzoate (VII), which by pyrolysis at 250—320° gave a 20% yield of 3β : 17β-diacetoxyandrost-6-ene (VIII). Introduction of the 6-double bond produced a molecular-rotation difference of −426°; in the case of 3β-acetoxycholest-6-ene a difference of −441° was reported (Barton and Rosenfelder, *loc. cit.*). Alkaline hydrolysis of (VIII) gave androst-6-ene-3β : 17β-diol (IX), which was converted by successive bromination, oxidation with chromium trioxide–acetic acid, and debromination to androst-6-ene-3 : 17-dione (X).

Partial hydrolysis of (VIII) with potassium carbonate gave 17β-acetoxyandrost-6-en-3β-ol (XI), which was converted into the Δ^6-analogue of testosterone acetate, namely, 17β-acetoxyandrost-6-en-3-one (XII) by oxidation of the dibromide with chromium trioxide–acetic acid and subsequent debromination.

Androst-6-ene-3β : 17β-diol (IX) and -3 : 17-dione (X), and 17β-acetoxyandrost-6-en-3-one (XII), together with the related compounds Δ^6-testosterone, androsta-4 : 6-diene-3 : 17-dione, and androsta-1 : 4 : 6-triene-3 : 17-dione, which may be expected to possess androgenic activity, the œstrogen 1-methyl-19-nor-Δ^6-œstrone, and the gestagen Δ^6-progesterone, have been sent to Professor A. Haddow, The Royal Cancer Hospital, for biological testing on the rate of growth of the Walker rat carcinoma. Δ^6-Progesterone exhibited a weakly positive effect in this test; further results will be published by Professor Haddow.

Experimental

For general experimental directions see preceding paper. Microanalyses are by Drs. Weiler and Strauss, Oxford.

3β : 17β-*Diacetoxyandrostan-7-one* (III).—3β : 17β-Diacetoxyandrost-5-en-7-one (II) (1·2 g.; m. p. 220°), prepared from 3β : 17β-diacetoxyandrost-5-ene by the method of Butenandt *et al.* (*Ber.*, 1938, **71**, 1316), was hydrogenated in ethyl acetate (40 c.c.) with platinum oxide (30 mg.); 1 mol. of hydrogen was absorbed in 2 hr., whereafter uptake ceased. Filtration from the catalyst, removal of solvent, and crystallisation of the residue from ethanol yielded 3β : 17β-*diacetoxyandrostan-7-one* (0·90 g.), m. p. 195—197°, $[\alpha]_D$ −41° ± 2° (*c* = 1·19)* (Found, after drying at 20°/0·01 mm.: C, 70·5; H, 8·8. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·8%). An additional quantity (0·21 g.), m. p. 190—192°, was obtained from the mother-liquors. The *semicarbazone* had m. p. 274—276° (Found, after drying at 100°/0·01 mm. for 1 hr.: N, 8·9. $C_{24}H_{37}O_5N_3$ requires N, 9·4%).

3β : 17β-*Diacetoxyandrostan-7α-ol* (IV*a*).—3β : 17β-Diacetoxyandrostan-7-one (1 g.) was hydrogenated with platinum oxide (60 mg.) in acetic acid (20 c.c.); 1 mol. of hydrogen was absorbed in 3 hr. After removal of the catalyst, acetic acid was evaporated off in a vacuum, and the residue dissolved in ether, washed with 2N-sodium carbonate and water, and dried. After evaporation, crystallisation from acetone–hexane yielded 3β : 17β-*diacetoxyandrostan-7α-ol*, m. p. 188—190°, $[\alpha]_D$ −21° ± 2° (*c* = 2·37)* (Found, after drying at 60°/0·01 mm. for 18 hr.: C, 70·15; H, 9·0. $C_{23}H_{36}O_5$ requires C, 70·35; H, 9·25%). The alcohol was benzoylated in pyridine at 15° for 24 hr. but the product could not be crystallised.

3β : 17β-*Diacetoxyandrostan-6-one* (V).—3β : 17β-Diacetoxyandrost-5-ene (I) (m. p. 159—

* Heusler and Wettstein (*Helv. Chim. Acta*, 1952, **35**, 284) have since recorded m. p. 193°, $[\alpha]_D$ −39° ± 4°, and m. p. 186°, $[\alpha]_D$ − 15° ± 4° respectively.

161°; 5·3 g.) was dissolved in acetic acid (75 c.c.), and fuming nitric acid (30 c.c.) was added in portions with cooling. Sodium nitrite (3·0 g.) was added in small portions during 1 hour at < 22°. The mixture was poured into water; the precipitated 3β : 17β-diacetoxy-6-nitro-androst-5-ene, when washed with water and dried in a vacuum-desiccator, had m. p. 85—95°, but could not be recrystallised. The crude 6-nitro-compound was dissolved in acetic acid (24 c.c.) containing water (5 c.c.), and zinc dust (10 g.) was added in portions; the solution became warm and was refluxed for 4 hr., cooled, and filtered, the filtrate partially evaporated in a vacuum, and the product poured into water. The crystalline ketone was dried and recrystallised from methanol, to yield material (2·9 g.), m. p. 164—176°. Repeated recrystallisation from methanol gave 3β : 17β-*diacetoxyandrostan-6-one*, m. p. 176—178°, $[\alpha]_D$ −37° ± 2° (*c* = 3·58) (Found, after drying at 20°/0·05 mm. for 16 hr.: C, 70·5; H, 8·75. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·8%). The mother-liquors from several reductions were combined and chromatographed on aluminium oxide with elution by benzene and benzene–ether (4 : 1) to give additional material.

3β : 17β-*Diacetoxyandrostan-6β-ol* (VI*a*).—3β : 17β-Diacetoxyandrostan-6-one (6·7 g.) in ethyl acetate (150 c.c.) was shaken with platinum oxide (600 mg.) in hydrogen; 0·78 mol. of hydrogen was absorbed in 90 min. whereafter absorption became very slow. After filtration from the catalyst and evaporation in a vacuum, the residue was chromatographed on aluminium oxide (180 g.) in benzene–pentane (1 : 2) with 600-c.c. eluant batches. Pentane–benzene (1 : 1) (2 fractions) and then benzene (fraction 3) removed mainly the starting ketone. Further elution with benzene (fractions 4—6) gave material, m. p. 110—125° (1·23 g.), and elution with ether–benzene (1 : 4) (fractions 7—9) gave material of m. p. 100—125° (3·25 g.). Fractions 4—9 were united and recrystallised from hexane, to yield 3β : 17β-*diacetoxyandrostan-6β-ol*, m. p. 128—130°, $[\alpha]_D$ −30° ± 2° (*c* = 2·17) (Found, after drying at 20°/0·01 mm. for 16 hr.: C, 70·45; H, 9·25. $C_{23}H_{36}O_6$ requires C, 70·35; H, 9·25%). Oxidation of the alcohol with chromium trioxide yielded the ketone (V), m. p. 176—178°, mixed m. p. 176—178°. Acetylation with pyridine–acetic anhydride at 20° gave 3β : 6β : 17β-*triacetoxyandrostane* (VI*b*), needles (from pentane), m. p. 74—75°, $[\alpha]_D$ −26° ± 4° (*c* = 0·65) (Found, after drying at 25°/0·05 mm. for 18 hr.): C, 69·0; H, 8·95. $C_{25}H_{38}O_6$ requires C, 69·05; H, 8·8%), alkaline hydrolysis of which yielded androstane-3β : 6β : 17β-triol (VI*c*), which forms a *hydrate*, m. p. 135° with immediate resolidification and final melting at 222—224° after crystallisation from benzene, $[\alpha]_D$ −8° ± 3° (*c* = 0·89). The substance could not be satisfactorily dried and a good analysis could not be obtained for the anhydrous triol (Found, after drying at 20°/0·01 mm. for 11 hr.: C, 70·0; H, 10·1. $C_{19}H_{32}O_3,H_2O$ requires C, 69·9; H, 10·5%).

Androstane-3β : 6α : 17β-*triol*.—3β : 17β-Diacetoxyandrostan-6-one (138 mg.) was dissolved in *n*-propanol (10 c.c.), and sodium (0·6 g.) added to the refluxing solution during 1 hr. The resulting solution was cooled and neutralised with 2N-hydrochloric acid, most of the propanol removed by distillation in a vacuum, and the residue diluted with water to yield androstane-3β : 6α : 17β-triol, m. p. 244—246° after crystallisation from benzene, $[\alpha]_D$ +27° ± 2° (*c* = 1·72). Satisfactory analytical results could not be obtained on account of its hygroscopic nature (Found, after sublimation at 200°/0·01 mm.: C, 67·2; H, 9·7%). Acetic anhydride–pyridine at 20° yielded 3β : 6α : 17β-*triacetoxyandrostane*, m. p. 64—68° after crystallisation from aqueous methanol, $[\alpha]_D$ +19° ± 2° (*c* = 1·77) (Found, after drying at 25°/0·05 mm. for 18 hr.: C, 69·15; H, 8·85. $C_{25}H_{38}O_6$ requires C, 69·05; H, 8·8%).

3β : 17β-*Dicetoxyandrostan-6β-yl Benzoate* (VII).—3β : 17β-Diacetoxyandrostan-6β-ol (VI*a*) (5·3 g.) was dissolved in dry pyridine (20 c.c.), benzoyl chloride (5 c.c.) added, and the mixture set aside at 20° for 24 hr. The solution was poured into water and next morning was extracted with ether; the ethereal solution was washed with 2N-hydrochloric acid, 2N-sodium carbonate, and water, dried, and evaporated. The amorphous residue did not readily crystallise, but after filtration in benzene through aluminium oxide the product crystallised from ether, to yield crude 3β : 17β-*diacetoxyandrostan-6β-yl benzoate*, m. p. 94—100°; recrystallisation from ether raised the m. p. to 101°, $[\alpha]_D$ −67° ± 2° (*c* = 3·84) (Found, after drying at 20°/0·05 mm. for 18 hr.: C, 72·7; H, 8·05. $C_{30}H_{42}O_6$ requires C, 72·55; H, 8·1%).

3β : 17β-*Diacetoxyandrost-6-ene* (VIII).—3β : 17β-Diacetoxyandrostan-6β-yl benzoate (5·3 g.) was heated in a distillation flask in a stream of carbon dioxide at 16 mm.; when the bath-temperature reached 310°, the bath was removed, the flask heated with a naked flame, and the contents distilled rapidly at 0·05 mm. The distillate, partly crystalline, was dissolved in ether, and the ethereal solution washed with 2N-sodium carbonate and water, dried, and evaporated. The residue (4 g.) crystallised from benzene–pentane (1 : 4), yielding 3β : 17β-diacetoxyandrost-6-ene (615 mg.), m. p. 174—178°. The mother-liquor was evaporated and the amorphous residue (3·4 g.) chromatographed on aluminium oxide (120 g.) prepared in benzene–pentane (1 : 4) with

eluant batches of 350 c.c. Elution with benzene–pentane (1 : 4 and 2 : 5) yielded uncrystallisable oils probably containing androsta-2 : 6-dien-17β-yl acetate, androsta-6 : 16-dien-3β-yl acetate, and possibly androsta-2 : 6 : 16-triene. The first eluate obtained with benzene–pentane (1 : 1) was oily, but the subsequent 5 fractions obtained with this mixture crystallised (m. p. 165—173°); these fractions were united and recrystallised from acetone, to give 3β : 17β-*diacetoxyandrost*-6-*ene*, m. p. 176—180° (total yield 20%). For analysis a specimen, recrystallised from ethanol, m. p. 178—180°, $[\alpha]_D$ −116° ± 2° (*c* = 4·56), giving a yellow colour with tetranitromethane–chloroform, was used (Found, after drying at 20°/0·05 for 16 hr.: C, 74·0; H, 9·2. $C_{23}H_{34}O_4$ requires C, 73·75; H, 9·15%).

Hydrolysis of the diacetate with potassium hydroxide in methanol yielded androst-6-ene-3β : 17β-diol (IX), m. p. 181—182° after crystallisation from hexane, $[\alpha]_D$ = −121° ± 2° (*c* = 1·02). Satisfactory analytical results could not be obtained for this substance which appeared to be hygroscopic (Found, after sublimation at 160°/0·01 mm.: C, 77·1, 76·4, 76·1; H, 10·3, 10·1, 10·8. Calc. for $C_{19}H_{30}O_2$: C, 78·6; H, 10·4%).

Androst-6-*ene*-3 : 17-*dione* (X).—To androst-6-ene-3β : 17β-diol (477 mg.) in acetic acid (40 c.c.), bromine in acetic acid was added dropwise until the colour was no longer discharged. A 4% solution of chromium trioxide in 95% acetic acid (9 c.c.) was then added and the mixture kept at 20° for 18 hr. Excess of chromic acid was destroyed with methanol, and the acetic acid largely removed at 30° in a vacuum. The precipitate obtained on addition of a large volume of water was filtered off, washed with water, and dried in a vacuum-desiccator; it was then debrominated with zinc dust in acetic acid at 100° for 15 min. After removal of zinc the filtrate was evaporated to small volume in a vacuum and diluted with water. The crystalline product was dissolved in benzene and filtered through aluminium oxide; crystallisation from ethanol gave *androst*-6-*ene*-3 : 17-*dione* (362 mg.), m. p. 165—167°, $[\alpha]_D$ −31° ± 2° (*c* = 1·78) (Found, after drying at 20°/0·05 for 18 hr.: C, 79·5; H, 9·3. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·15%). The diketone was characterised by the *dioxime*, m. p. 257—258° after crystallisation from ethyl acetate (Found, after drying at 20°/0·05 mm. for 16 hr.: N, 8·3. $C_{19}H_{28}O_2N_2$ requires N, 8·85%).

17β-*Acetoxyandrost*-6-*en*-3β-*ol* (XI).—3β : 17β-Diacetoxyandrost-6-ene (V) (363 mg., 0·97 mmole) in methanol (30 c.c.) was treated with potassium carbonate (70 mg., 0·51 mmole) in water (2·0 c.c.) and methanol (4·0 c.c.), and the solution set aside at 15° for 18 hr. The small amount of residual potassium carbonate was neutralised with acetic acid and the solvent removed in a vacuum; the residue was dissolved in ether and the ethereal solution washed with sodium hydrogen carbonate solution and with water, dried, and evaporated. The product was chromatographed on aluminium oxide (9 g.) prepared in benzene–pentane (1 : 4); elution with benzene and with ether–benzene (1 : 5) yielded the crude monoacetate (138 mg.) which, recrystallised from hexane, gave 17β-*acetoxyandrost*-6-*en*-3β-*ol* (107 mg.), m. p. 150—152°, $[\alpha]_D$ −130° ± 2° (*c* = 1·05) (Found, after sublimation at 140°/0·05 mm.: C, 76·0; H, 9·5. $C_{21}H_{32}O_3$ requires C, 75·85; H, 9·7%).

17β-*Acetoxyandrost*-6-*en*-3-*one* (XII).—To 17β-acetoxyandrost-6-en-3β-ol (368 mg.) in acetic acid (12 c.c.), bromine in acetic acid was added until a faint yellow colour persisted; a 4% solution of chromium trioxide in 95% acetic acid (3·0 c.c.) was then added and the mixture kept at 15° for 18 hr. Excess of chromium trioxide was destroyed with methanol, and the solution evaporated at 30° in a vacuum and diluted with water; the precipitated dibromo-diketone was filtered off, washed with water, and dried in a vacuum-desiccator. Debromination was effected by zinc dust in acetic acid at 100° (15 min.); the product, dissolved in benzene, was filtered through aluminium oxide and crystallised from ethanol, to give 17β-*acetoxyandrost*-6-*en*-3-*one* (263 mg.), m. p. 153—155°, $[\alpha]_D$ −96° ± 2° (*c* = 1·24) (Found, after drying at 20°/0·05 mm. for 15 hr.: C, 76·6; H, 9·2. $C_{21}H_{30}O_3$ requires C, 76·35; H, 9·15%).

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51. *Synthetical and Stereochemical Investigations of Reduced Cyclic Bases. Part III.* The Synthetic* cis- *and* trans-*Octahydroindoles and the Anomalous Exhaustive Methylation Products of the* trans-*Base.*

By F. E. King, (Miss) D. M. Bovey, K. G. Mason, and R. L. St. D. Whitehead.

Syntheses are described, from *cyclo*hexane derivatives of known stereochemical structure, of both *cis*- and *trans*-octahydroindole. The *cis*-configuration provisionally attributed (King, Barltrop, and Whalley, *J.*, 1945, 277) to the octahydro- and octahydro-*N*-methyl-indoles obtained by catalytic reduction of indole has thus been confirmed.

trans-Octahydrodimethylindolinium iodide is converted by Hofmann's procedure into an unsaturated amine $C_{10}H_{19}N$ and a dibasic ether $C_{20}H_{40}ON_2$. Reduction of the unsaturated base gives a product $C_{10}H_{21}N$ isomeric but not identical with either of the predictable alternatives, *viz.*, 2-dimethylaminoethyl*cyclo*hexane, $Me_2N{\cdot}CH_2{\cdot}CH_2{\cdot}C_6H_{11}$, or *trans*-2-ethyl-*NN*-dimethyl*cyclo*hexylamine, $Me_2N{\cdot}C_6H_{10}Et$.

The catalytic hydrogenation of indole (Willstätter and Jacquet, *Ber.*, 1918, **51**, 777; Adkins and Coonradt, *J. Amer. Chem. Soc.*, 1941, **63**, 1563) affords an octahydro-derivative in which, for reasons outlined in Part I (King, Barltrop, and Whalley, *J.*, 1945, 277), the constituent rings were assumed to have the *cis*-configuration. An octahydro-*N*-methylindole obtained by reduction of indole over Raney nickel in methanol (Part I) was likewise regarded as a member of the *cis*-series, but no data were available from which it was possible to determine the precise configuration of these reduction products or even to confirm their relationships.

The problem has therefore been investigated by synthesis, and, as in the case of the decahydroquinolines (King, Henshall, and Whitehead, *J.*, 1948, 1373), the two stereoisomeric octahydroindoles have now been obtained by ring-closure of the appropriate *cyclo*hexane derivatives of known configuration. The assumed *cis*-configuration of the octahydro- and the octahydro-*N*-methyl-indoles previously prepared has thereby been confirmed; a minor by-product sometimes found in the Raney nickel–methanol hydrogenation has been identified as the *trans*-*N*-methyl base.

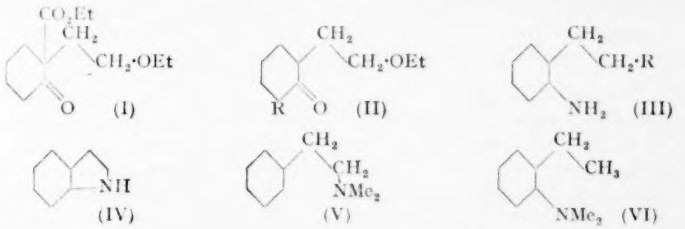
First, 2-ethoxyethyl bromide was condensed with ethyl sodio-2-keto*cyclo*hexanecarboxylate in alcohol, but whereas 3-ethoxypropyl bromide yielded 66% of the substituted keto-ester (Part II), only diethyl α-2-ethoxyethylpimelate, $EtO_2C{\cdot}[CH_2]_4{\cdot}CH(CO_2Et){\cdot}[CH_2]_2{\cdot}OEt$, was obtained under these conditions. When, however, this difficulty was overcome by employing toluene as solvent, ketonic hydrolysis of the resulting ester (I) was much reduced by partial ring-fission to the substituted pimelic acid. It was found better, therefore, to perform the synthesis with alcohol and afterwards to recyclise the resulting pimelic ester, the product, presumably (II; R = CO_2Et) (cf. Openshaw and Robinson, *J.*, 1937, 945), being hydrolysed to the ketone (II; R = H) without difficulty.

Reduction of the ketoxime with sodium in alcohol afforded an amine which in its production under alkaline conditions is presumed from Skita's generalised observation (see Part I) to be the *trans*-2-2′-ethoxyethyl*cyclo*hexylamine (III; R = OEt). In boiling hydrobromic acid the ethoxy-group was replaced by bromine, giving a homogeneous crystalline hydrobromide of *trans*-2-2′-bromoethyl*cyclo*hexylamine (III; R = Br) which after liberation from its salt with alkali underwent ring closure to the hitherto unknown *trans*-octahydroindole (IV), a liquid characterised by several crystalline derivatives.

When heated in a sealed tube with ammonium formate (Leuckart reaction) the ethoxyethyl*cyclo*hexanone (II; R = H) was converted into an oily mixture of stereoisomers, principally the *cis*-2-2′-ethoxyethyl-*N*-formyl*cyclo*hexylamine. The formation of both isomers was also observed in the corresponding stage of the *cis*-decahydroquinoline synthesis (Part II).

* Part II, *J.*, 1948, 1373.

Part of the oily product was hydrolysed with dilute hydrochloric acid and the *cis*-2-2′-ethoxyethyl*cyclo*hexylamine purified by fractional crystallisation of the picrolonate. Both the regenerated amine and remaining formamide were then converted into the bromo-amine hydrobromide, in contrast to its *trans*-isomer, an uncrystallisable syrup, and hence into *cis*-octahydroindole. The melting points of the benzenesulphonamide and picrate of both specimens agreed with those recorded for the corresponding products from the octahydro-base prepared by the hydrogenation of indole (Willstätter; Adkins), and the picrolonate showed no depression of melting point with the specimen described in Part I.



Determinations of density and refractive index were made on both the *cis*- and the *trans*-amine, after purification through suitable salts. In agreement with the Auwers rule (see Part I) the constants of the *cis*-octahydroindole are slightly greater than those of the *trans*-isomer.

It has been shown (Part I) that the octahydro-*N*-methyl- and -*N*-ethyl-indole which are formed when indole is hydrogenated respectively in methanol and ethanol can be prepared more readily than the unalkylated base, and the exhaustive methylation data already published were ascertained from experiments on the resulting octahydro-*N*-methyl compound. When the *N*-methyl derivatives of both synthetic octahydroindoles were prepared by the formaldehyde–formic acid method, the methiodide and methopicrate of the *cis*-compound proved to be identical with those originating from the material formed by catalytic reduction in methanol.

An alternative synthesis of octahydroindole was investigated which was based on the existence of 2-2′-nitroethyl*cyclo*hexanone, prepared from 2-dimethylaminomethyl*cyclo*hexanone and nitromethane by Reichert and Posemann (*Arch. Pharm.*, 1937, **275**, 67). Neutral catalytic reduction of the nitro-ketone resulted, even before isolation of the product, in ring-closure to a hexahydroindole. This was resistant to further hydrogenation over catalysts but could be saturated by treatment with sodium in alcohol. Being an alkaline reduction, it might possibly have given a *trans*-product, but, with the fused dicyclic system pre-existent in the molecule, the greater stability of the *cis*-configuration is evidently the deciding factor in the reduction, since the octahydroindole obtained in this experiment proved to be the *cis*-isomeride.

In the earlier stages of this enquiry (Part I) exhaustive methylation was applied to the octahydro-*N*-methylindole obtained by reduction, in the belief that an *NN*-dimethyl-2-vinyl*cyclo*hexylamine would be obtained which would reveal the stereochemical configuration of the octahydro-compound by giving, when saturated, either the *cis*- or the *trans*-2-ethyl-*NN*-dimethyl*cyclo*hexylamine (VI) synthesised at that time as reference compounds. This impression was based on the behaviour of the decahydroquinolines and of octahydro-2-methylindole in the exhaustive methylation process, but, in contrast, the octahydroindole yielded an unsaturated base which by its reduction to 2-dimethylaminoethyl*cyclo*hexane (V) proved that the link from the nitrogen to the *cyclo*hexane ring had been severed. This has been confirmed in the present work, during which the exhaustive methylation of the *trans*-compound has also been examined and found to give an unsaturated amine $C_{10}H_{19}N$ and a higher-boiling product $C_{20}H_{40}ON_2$. The latter was a saturated diacidic base, and with boiling hydrobromic acid was hydrolysed to a crystalline bromo-amine hydrobromide $C_{10}H_{20}NBr,HBr$, thus showing it to be an ether. The more volatile substance readily yielded a dihydro-base $C_{10}H_{21}N$, but from the properties of the picrate, picrolonate, and methiodide of the reduced product it was clearly not 2-dimethylaminoethyl*cyclo*-

hexane. On the other hand, it was also not identical with either *trans*- or even the *cis*-2-ethyl-*NN*-dimethyl*cyclo*hexylamine (VI), whence it follows that the transformation has been attended by further molecular rearrangement. To provide products for direct comparison the synthesis of the two stereoisomeric 2-ethyl-*NN*-dimethyl*cyclo*hexylamines has also been repeated. The salt, m. p. 182°, previously described as the *trans*-amine methiodide (Part I) was shown to be the tertiary amine hydriodide, the authentic methiodide having m. p. 231° (decomp.).

The structure of the exhaustive methylation products of *trans*-octahydroindole will be discussed in a further communication.

Experimental

Ethyl 1-2′-*Ethoxyethyl*-2-*keto*cyclo*hexanecarboxylate* (I).—To the suspension of sodium salt formed in 2 hours from ethyl 2-keto*cyclo*hexanecarboxylate (52 g.) and powdered sodium (6·5 g.) in boiling xylene (250 c.c.), 2-ethoxyethyl bromide (43·5 g.) was added, and refluxing continued for 12—15 hours. When cooled, washed with dilute acid, dried and distilled, the xylene solution yielded a fraction, b. p. 147—167°/12 mm., from which was obtained the keto-ester (I) (33·6 g., 49%), b. p. 152—158°/10 mm. Its *semicarbazone*, rods from ethyl acetate–light petroleum, has m. p. 128° (Found : C, 56·3; H, 8·5; N, 14·2. $C_{14}H_{25}O_4N_3$ requires C, 56·3; H, 8·4; N, 14·0%).

Diethyl α-2-*Ethoxyethylpimelate*.—The mass of salt formed from ethyl 2-keto*cyclo*hexanecarboxylate (200 g.) and a solution of sodium (27 g.) in ethanol (360 c.c.) was refluxed for 4 hours with 2-ethoxyethyl bromide (216 g.) and then for another 2 hours after a further addition of sodium (4·7 g.) in alcohol (70 c.c.). Solvent was then distilled off and the residue treated with water, etc., to give the product (155—165 g.), b. p. *ca.* 175°/9 mm., refractionated to give the pure *pimelate* (Found : C, 62·5; H, 9·8. $C_{15}H_{28}O_5$ requires C, 62·5; H, 9·8%). Hydrolysis with boiling 30% barium hydroxide gave α-2-*ethoxyethylpimelic acid* b. p. 238—242°/7 mm. (Found : C, 56·5; H, 8·6. $C_{11}H_{20}O_5$ requires C, 56·9; H, 8·7%).

2-2′-*Ethoxyethyl*cyclo*hexanone* (II; R = H).—(*a*) Diethyl α-2-ethoxyethylpimelate (160 g.) was added to sodium (25 g.) dispersed in xylene (500 c.c.), and the condensation initiated with ethanol (1—2 c.c.). When the reaction moderated, the mixture was refluxed for 2 hours and then poured into dilute acid and ice. The oil isolated from the xylene layer was hydrolysed under reflux with barium hydroxide solution (385 g. in 1100 c.c.) for 6 hours. Acidification and extraction with ether gave the ketone (68 g.), b. p. 127—129°/15 mm., characterised by its *semicarbazone*, needles (from water), m. p. 126° (Found : C, 58·1; H, 9·1; N, 18·3. $C_{11}H_{21}O_2N_3$ requires C, 58·1; H, 9·3; N, 18·5%), and by the 2 : 4-*dinitrophenylhydrazone*, m. p. 75° (Found : C, 54·5; H, 6·5; N, 16·0. $C_{16}H_{22}O_5N_4$ requires C, 54·8; H, 6·3; N, 16·0%).

(*b*) The 2-keto*cyclo*hexanecarboxylate (I) (15·7 g.) was heated under reflux with barium hydroxide (36 g.) in water (100 c.c.) for 6 hours. The oil liberated on acidification was dissolved in ether and then washed with 10% aqueous sodium hydroxide, thus leaving the ketone (II; R = H) (2·2 g., 20%), b. p. 105—110°/10 mm., identified by its derivatives. The sodium hydroxide washings contained α-2-ethoxyethylpimelic acid (3·1 g., 20%), b. p. 238—242°/77 mm. (Found : C, 56·5; H, 8·6%).

2-2′-*Ethoxyethyl*cyclo*hexanone Oxime*.—The optimum yield of the *oxime*, obtained from hydroxylamine hydrochloride (15 g.), sodium acetate (30 g.), and the ketone (II; R = H) (34 g.) in 60% aqueous alcohol (220 c.c.), was 78% ; the derivative had b. p. 176—179°/29 mm. (Found : C, 64·9; H, 10·3; N, 7·2. $C_{10}H_{19}O_2N$ requires C, 64·8; H, 10·3; N, 7·6%).

trans-2-2′-*Ethoxyethyl*cyclo*hexylamine* (III; R = OEt).—Sodium (40 g.) was added in portions to a boiling solution of the ketoxime (29 g.) in ethanol (250 c.c.); afterwards, a slight excess of acid was introduced and the alcohol evaporated under reduced pressure. By-products were removed by ether and then the trans-*amine* (III; R = OEt) was liberated by concentrated potassium hydroxide as an oil (19·1 g., 71%), b. p. 116—118°/18 mm. It formed a *picrate*, m. p. 100°, from water (Found : C, 47·8; H, 6·1; N, 13·8. $C_{10}H_{21}ON,C_6H_3O_7N_3$ requires C, 48·0; H, 6·0; N, 14·0%), and a *picrolonate*, m. p. 180°, as needles from ethanol (Found : C, 55·3; H, 6·6; N, 16·1. $C_{10}H_{21}ON,C_{10}H_8O_5N_4$ requires C, 55·1; H, 6·7; N, 16·1%). The *benzoyl* derivative separated from light petroleum or ethanol as a crystalline mass, m. p. 120° (C, 74·5; H, 8·7; N, 4·9. $C_{17}H_{25}O_2N$ requires C, 74·1; H, 9·1; N, 5·1%).

trans-2-2′-*Bromoethyl*cyclo*hexylamine Hydrobromide*.—The *trans*-amine (III; R = OEt) (21 g.) was refluxed with 50% hydrobromic acid (800 c.c.) for 7 hours. After distillation of the acid under reduced pressure, the residue solidified, and crystallisation from ethyl acetate

or acetone gave the *hydrobromide* of the *trans*-bromo-amine (III; R = Br) as needles, m. p. 191° (Found: C, 33·2; H, 6·3; N, 5·0; Br, 56·1. $C_8H_{16}NBr,HBr$ requires C, 33·5; H, 5·9; N, 4·9 Br, 55·7%). A *picrate*, prepared by mixing aqueous solutions of the salt and of picric acid, crystallised from benzene–ethyl acetate in yellow needles, m. p. 118° (Found: C, 38·9; H, 4·4 N, 13·0; Br, 18·4. $C_8H_{16}NBr,C_6H_3O_7N_3$ requires C, 38·6; H, 4·4; N, 12·9; Br, 18·4%).

trans-*Octahydroindole* (IV).—The hydrobromide of the *trans*-bromide (III; R = Br) (32·5 g.) was dissolved in water (200 c.c.) and added during 2 hours to a cold stirred solution of sodium hydroxide (25 g.) in water (150 c.c.). After a further 1½ hours the product was extracted with ether, and distillation gave *trans*-octahydroindole (11·65 g., 82%) as a colourless oil, b. p. 72—73°/19 mm. It formed the following derivatives: *picrolonate*, yellow-orange prisms, m. p. 234°, from ethanol (Found: C, 55·3; H, 6·0; N, 18·0. $C_8H_{15}N,C_{10}H_8O_5N_4$ requires C, 55·6; H, 5·9; N, 18·0%); *picrate*, crystallising from benzene in yellow rhombohedra, m. p. 147° (Found: C, 47·2; H, 5·1; N, 15·5. $C_8H_{15}N,C_6H_3O_7N_3$ requires C, 47·5; H, 5·1; N, 15·8%); *benzenesulphonamide*, prisms, m. p. 62—63°, from light petroleum (Found: C, 63·3; H, 7·2; N, 5·4. $C_{14}H_{19}O_2NS$ requires C, 63·4; H, 7·2; N, 5·3%); 3 : 5-*dinitrobenzoate*, prepared in alcohol and separating from ethyl acetate as a microcrystalline mass, m. p. 178° (Found: C, 53·6; H, 5·6; N, 13·0. $C_{15}H_{19}O_6N_3$ requires C, 53·4; H, 5·6; N, 12·5%). A sample of *trans*-octahydroindole purified through the picrate had b. p. (Siwoloboff) 186·0°/767 mm., d_4^{24} 0·930, n_D^{24} 1·484, $[M]_R$ 38·45 (Calc., 38·34).

cis-2-2′-*Ethoxyethyl*cyclo*hexylamine*.—The ketone (II; R = H) (25 g.) was heated with ammonium formate (48 g.) in sealed tubes at 200° for 10 hours. After the addition of water, the formamide (23 g., 78%), b. p. 196—202°/17 mm., was isolated with ether, and a portion (5 g.) refluxed with 3% hydrochloric acid (25 c.c.) for 15 minutes. The clear solution was basified with potassium hydroxide and the extracted mixed amines (1·7 g.), b. p. 119°/17 mm., were treated with picrolonic acid (2·6 g.) in hot ethanol (66 c.c.). The picrolonate (0·7 g.), m. p. and mixed m. p. 180°, which separated on cooling was of the *trans*-amine (II; R = OEt). The addition of water then precipitated the *cis*-amine *picrolonate* crystallising from ethyl acetate as orange cubes (2·8 g.), m. p. 148° (Found: C, 54·8; H, 6·5; N, 16·3%).

cis-*Octahydroindole*.—(*a*) The picrolonate of the *cis*-amine (III; R = OEt), dissolved in ethanol (10 c.c.), was shaken with warm 40% aqueous potassium hydroxide (40 c.c.). The suspension was shaken with ether, and the extracted oil refluxed for 5 hours with 50% hydrobromic acid. When evaporated under reduced pressure the solution left a syrupy product; it was shaken for several hours with aqueous ammonia and ether. The amine (0·6 g.) extracted from the ether with acid and then precipitated by alkali gave a picrolonate as spherical clusters (from ethanol), m. p. 218°, undepressed by the picrolonate of octahydroindole obtained by catalytic reduction (Part I) (Found: C, 55·5; H, 6·0; N, 17·8%).

(*b*) The formamide (10 g.), b. p. 196—202°, from the Leuckart reaction similarly treated with boiling hydrobromic acid (400 c.c.) gave a syrupy hydrobromide. It was cyclised as above with aqueous ammonia and the resulting base (2·5 g., 40%), b. p. 73—76°/18 mm., identified by the picrolonate, m. p. 218°; the method using sodium hydroxide which gave 82% of the *trans*-amine was not devised until later. In addition to the picrolonate, *cis*-octahydroindole gave the following derivatives: picrate, yellow prisms, m. p. 137°, from benzene (Willstätter, Seitz, and von Braun, *Ber.*, 1925, **56**, 385, give m. p. 137°), mixed m. p. with the *trans*-picrate 111—120° (Found: C, 47·2; H, 4·9; N, 16·1. $C_8H_{15}N,C_6H_3O_7N_3$ requires C, 47·5; H, 5·1; N, 15·8%); *benzenesulphonamide*, colourless spiky needles, m. p. 70° and 59—62° mixed with the *trans*-isomer (Willstätter *et al.*, 70—71°; Adkins and Coonradt, *loc. cit.*, 69·5—70·5°) not previously analysed (Found: C, 63·2; H, 7·1; N, 4·9; S, 11·7. $C_{14}H_{19}O_2NS$ requires C, 63·5; H, 7·2; N, 5·3; S, 12·1%); 3 : 5-*dinitrobenzoate* (from ethyl acetate), m. p. 192°, and 160—186° mixed with the *trans*-isomer (Found: C, 53·0; H, 5·6; N, 12·4%). A sample of *cis*-octahydroindole purified through the 3 : 5-dinitrobenzoate had b. p. (Siwoloboff) 187·5°/767 mm., d_4^{18} 0·945, n_D^{19} 1·4899, $[M]_R$ 38·24 (Calc., 38·34) (Willstätter *et al.* give b. p. 185·5°/760 mm., d_4^{24} 0·9472, n_D^{20} 1·4892, and Adkins and Coonradt, n_D^{25} 1·4833.

trans-*Octahydro-N-methylindole*.—*trans*-Octahydroindole (5 g.) was refluxed for 4 hours with a mixture of 40% aqueous formaldehyde (5 g.) and 90% formic acid (6·5 g.). *trans*-Octahydro-*N*-methylindole (3·5 g.), b. p. 54—55°/8 mm., was isolated by basifying the solution and extracting it with ether. It afforded the following derivatives: *picrate*, crystallising from ethanol in yellow needles, m. p. 196° (Found: C, 48·6; H, 5·5; N, 15·1. $C_9H_{17}N,C_6H_3O_7N_3$ requires C, 48·9; H, 5·4; N, 15·2%); *picrolonate*, orange-yellow aggregates, m. p. 182° (Found: C, 56·3; H, 6·1; N, 17·6. $C_9H_{17}N,C_{10}H_8O_5N_4$ requires C, 56·6; H, 6·2; N, 17·4%); *methiodide*, crystallising from acetone in plates, m. p. 229° (Found: C, 42·7; H, 7·1; N, 4·7; I, 43·9. $C_{10}H_{20}NI$ requires

C, 42·75; H, 7·1; N, 5·0; I, 45·2%); *methopicrate*, which crystallised from ethanol in orange prisms, m. p. 171° (Found: C, 50·4; H, 5·7. $C_{16}H_{22}O_7H_4$ requires C, 50·3; H, 5·8%); *bis*-3 : 5-*dinitrobenzoate*, which crystallised from ethyl acetate in needles, m. p. 129° (Found: C, 49·0; H, 4·4; N, 12·6. $C_{23}H_{25}O_{12}N_5$ requires C, 49·0; H, 4·4; N, 12·5%).

cis-*Octahydro*-N-*methylindole*.—(*a*) Prepared similarly to the *trans*-isomer, the cis-N-*methyl* base had b. p. 57°/9 mm. and was characterised by the following derivatives: *picrate*, yellow needles, m. p. 204°, from ethanol (Found: C, 48·8; H, 5·5; N, 14·9%); *picrolonate*, microcrystalline yellow mass, m. p. 168°, from ethanol (Found: C, 56·9; H, 6·3; N, 17·1%); *methiodide* crystallising in needles, m. p. 208°, from acetone–ether (Found: C, 43·1; H, 6·8; N, 4·7; I, 43·7%); *methopicrate*, foliated prisms, m. p. 195°, from ethanol, not depressed by the methopicrate, m. p. 194°, of the octahydro-*N*-methylindole prepared by catalytic reduction (Part I) (Found: C, 50·2; H, 5·5; N, 14·9. $C_{16}H_{22}O_7N_4$ requires C, 50·2; H, 5·8; N, 14·7%). The methiodide, m. p. 201° (Part I), is now known to have been contaminated with the less soluble *trans*-metho-salt, m. p. 229°. Up to 5% of *trans*-amine, calculated on methiodide, is sometimes present in the indole reduction product.

(*b*) *cis*-Amine was also derived from 2-2′-nitroethyl*cyclo*hexanone; the yield of nitro-ketone, reported by Reichert and Posemann (*loc. cit.*) to be 70% is, after distillation, 30%. The product, b. p. 126—129°/0·8 mm., gave the semicarbazone, m. p. 151—152°, described by these authors (Found: C, 47·0; H, 6·7. Calc. for $C_9H_{16}O_3N_4$: C, 47·5; H, 7·0%). The nitro-ketone was hydrogenated over Raney nickel at N.T.P. in 3—4 hours, and the product gave the *picrate* of a hexahydroindole, crystallising from ethanol in yellow prisms, m. p. 133° (Found: C, 47·4; H, 4·4; N, 15·7. $C_8H_{13}N,C_6H_3O_7N_3$ requires C, 47·7; H, 4·5; N, 15·9%). The base, b. p. 76°/11 mm., resinified on attempted reduction with amalgamated zinc and hydrochloric acid, and resisted hydrogenation over palladised charcoal. Without being isolated the product from the reduction of 7 g. of nitro-ketone was treated in alcohol (130 c.c.) with sodium (11 g.). After evaporation of solvent from the acidified solution *cis*-octahydroindole (1·2 g.; b. p. 72°/13 mm.) was isolated and identified by mixed m. p.s of the picrolonate, m. p. 218°, and 3 : 5-dinitrobenzoate, m. p. 192°.

trans-2-*Ethyl*-NN-*dimethyl*cyclo*hexylamine* (VI).—Repetition of the synthesis of this amine shows that it affords a *methiodide* which separates from acetone–ethyl acetate in plates, m. p. 231° (decomp.), not 182° as recorded in Part I (Found: C, 44·5; H, 7·9; N, 4·8; I, 43·1. $C_{11}H_{24}NI$ requires C, 44·4; H, 8·1; N, 4·7; I, 42·8%). The compound, m. p. 182°, is the trans-2-*ethyl*-NN-*dimethyl*cyclo*hexylamine hydriodide*, and the specimen incorrectly named in Part I had mixed m. p. 182° with a sample made from the tertiary base and hydriodic acid (Found: C, 42·4; H, 7·7; N, 4·8; I, 44·7. $C_{10}H_{21}N,HI$ requires C, 42·5; H, 7·8; N, 5·0; H, 45·0%). Also prepared were the *picrate*, yellow rhombohedra, m. p. 126°, from ethanol (Found: C, 50·3; H, 6·3; N, 14·5. $C_{10}H_{21}N,C_6H_3O_7N_3$ requires C, 50·0; H, 6·25; N, 14·8%), and the *picrolonate*, yellow square tablets, m. p. 170°, from ethanol (Found: C, 57·5; H, 6·7; N, 16·8. $C_{10}H_{21}N,C_{10}H_8O_5N_4$ requires C, 57·3; H, 7·0; N, 16·7).

cis-2-*Ethyl*-NN-*dimethyl*cyclo*hexylamine*.—The new sample of this amine gave a methiodide, m. p. 232° (decomp.) (recorded in Part I, 231°). The *picrate* crystallised from ethanol in yellow prisms, m. p. 159° (Found: C, 50·0; H, 6·7; N, 14·9%).

Exhaustive Methylation of trans-*Octahydroindole*.—A solution of the *trans*-methiodide, m. p. 229° (10 g.), in water (25 c.c.) was shaken in the dark with freshly prepared silver oxide (4·5 g.) for 3 hours. The filtered solution was then heated under reduced pressure, first at 50° and afterwards slowly to 100° at 10—12 mm. When distillation ceased, solid potassium hydroxide was added to the distillate which on ether-extraction yielded a base (0·9—2·3 g.), b. p. 65°/9 mm. It formed a *picrate* crystallising from ethanol in yellow flat prisms, m. p. 117—118° (Found: C, 50·4; H, 5·8; N, 14·5. $C_{10}H_{19}N,C_6H_3O_7N_3$ requires C, 50·2; H, 5·8; N, 14·7%), a *picrolonate*, yellow prisms, m. p. 163°, from aqueous ethanol (Found: C, 57·5; H, 6·5; N, 16·7. $C_{10}H_{19}N,C_{10}H_8O_5N_4$ requires C, 57·6; H, 6·5; N, 16·8%), and a *methiodide*, precipitated from acetone by ether, m. p. 203° (Found: C, 44·7; H, 7·3; N, 4·8; I, 43·6. $C_{11}H_{22}NI$ requires C, 44·7; H, 7·5; N, 4·8; I, 43·05%).

When dissolved in ethanol (30 c.c.) and neutralised with concentrated hydrochloric acid, the methine base (1 g.) was reduced at N.T.P. over palladised charcoal within 20 min. Isolation in the normal manner gave the dihydro-base (0·8 g.), b. p. 66°/9 mm., which formed a *picrate*, crystallising from ethanol in yellow needles, m. p. 106° (Found: C, 49·6; H, 6·3; N, 14·1. $C_{10}H_{21}N,C_6H_3O_7N_3$ requires C, 50·0; H, 6·25; N, 14·6%), a *picrolonate*, fine yellow needles, m. p. 160°, from ethanol (Found: C, 57·6; H, 6·9; N, 16·5. $C_{10}H_{21}N,C_{10}H_8O_5N_4$ requires C, 57·3; H, 7·0; N, 16·7%), and a *methiodide*, prisms, m. p. 221°, from acetone–ethyl

acetate (Found : C, 44·7; H, 8·0; N, 3·9; I, 42·0. $C_{11}H_{24}NI$ requires C, 44·4; H, 8·1; N, 4·7; I, 42·8%).

When distilled, the residue from which the methine-base had originally been evaporated was obtained as a colourless oil (1—2·1 g.), b. p. 130°/10 mm., insoluble in water [Found : C, 74·1; H, 12·4; N, 8·8%; *M* (Rast), 310. $C_{20}H_{40}ON_2$ requires C, 74·0; H, 12·4; N, 8·6%; *M*, 324]. It formed a *dipicrate*, yellow prisms, m. p. 161°, from ethanol (Found : C, 49·4; H, 5·7; N, 14·3. $C_{20}H_{40}ON_2,2C_6H_3O_7N_3$ requires C, 49·1; H, 5·9; N, 14·3%), identical with a specimen prepared from the base before distillation. Other derivatives of the *diamino-ether* prepared were the *dipicrolonate*, yellow needles, m. p. 181°, from acetone (Found : C, 56·3; H, 6·6; N, 16·3. $C_{20}H_{40}ON_2,2C_{10}H_8O_5N_4$ requires C, 56·2; H, 6·8; N, 16·4%), and *distyphnate* (Found : N, 13·7. $C_{20}H_{40}ON_2,2C_6H_3O_8N_3$ requires N, 14·1%).

The diamino-ether (1·5 g.) was heated under reflux with 50% hydrobromic acid (10 c.c.) for ½ hour, and the solution then evaporated under reduced pressure. The solid residue of *bromoamine hydrobromide* crystallised from acetone in needles (2·1 g., 72%), m. p. 167° (Found : C, 38·1; H, 6·8; Br, 51·5. $C_{10}H_{20}NBr,HBr$ requires C, 38·1; H, 6·7; Br, 50·7%).

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52. *Preparation of* N-*Substituted Amidines.*

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N-Monosubstituted amidines can be prepared in good yield by heating equimolecular quantities of a nitrile and a primary amine with an equivalent of sodium or sodamide. Acetonitrile and benzonitrile on treatment with aniline under the conditions of the Hoesch reaction afford the corresponding *N*-phenylamidines.

N-ARYLAMIDINES have recently been observed to exhibit high, selective activity *in vitro* against *Mycobacterium tuberculosis* (Partridge, *J.*, 1949, 2683, 3043; 1950, 2901; *J. Pharm. Pharmacol.*, 1952, **4**, 533; Cooper and Partridge, *J.*, 1950, 459; Charlton, Maliphant, Oxley, and Peak, *J.*, 1951, 485). Since relatively few methods are available for the preparation of these compounds in good yield and free from *NN'*-diarylamidines, we examined the reaction of arylamines with nitriles in the presence of sodium (Lottermoser, *J. pr. Chem.*, 1896, **54**, 113; von Walther and Grossmann, *ibid.*, 1908, **78**, 478).

Lottermoser (*loc. cit.*) concluded that this reaction may be represented by the equation

$$2R{\cdot}CN + Ar{\cdot}NH_2 + 2Na \longrightarrow R{\cdot}C(:NAr){\cdot}NH^-\}Na^+ + RH + NaCN$$

although no evidence was presented for the formation of the hydrocarbon, RH. We have confirmed these observations, and from *p*-tolunitrile have demonstrated the formation of toluene (characterised as benzoic acid). By analogy with the reaction of sodamide and a nitrile which affords an unsubstituted amidine (Cornell, *J. Amer. Chem. Soc.*, 1928, **50**, 3313; Ziegler, Rohm, and Haas, U.S.P. 2,049,582; Ziegler and Ohlinger, *Annalen*, 1932, **495**, 84; Kirsanov and Polyakova, *Bull. Soc. chim.*, 1936, **3**, 1600; Ewins, Barber, Newbery, Ashley, and Self, B.P. 538,463; Ewins and Ashley, B.P. 545,708; Newbery and Webster, *J.*, 1947, 738), it appeared likely that the production of the sodio-*N*-arylamidine involved the intermediate formation of a sodioarylamine :

$$Ar{\cdot}NH_2 + Na \longrightarrow Ar{\cdot}NH^-\}Na^+ + H \quad . \quad . \quad . \quad . \quad (1)$$

$$R{\cdot}CN + Ar{\cdot}NH^-\}Na^+ \longrightarrow R{\cdot}C(:NAr){\cdot}NH^-\}Na^+ \quad . \quad . \quad . \quad . \quad (2)$$

and that the hydrocarbon and sodium cyanide resulted from the reduction of the nitrile by hydrogen liberated in stage (1). In support of this it was found that sodioaniline, produced by heating aniline and sodamide in boiling benzene, afforded *N*-phenylbenzamidine in 64% yield on subsequent treatment with benzonitrile. When equimolecular

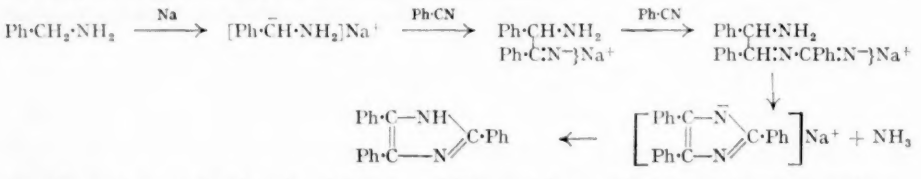
quantities of sodium, benzonitrile, and aniline were brought into reaction in benzene, *N*-phenylbenzamidine was formed in 77% yield; in addition, small quantities of ionisable cyanide, benzylamine, and benzaldehyde were found but no permanent gas was evolved and neither 1 : 2-dihydro-2 : 2 : 4 : 6-tetraphenyl-1 : 3 : 5-triazine nor kyaphenin was detected (cf. Anker and Cook, *J.*, 1941, 323; Swamer, Reynolds, and Hauser, *J. Org. Chem.*, 1951, **16**, 43). Benzylamine and benzaldehyde may have arisen by reduction of either the nitrile or the amidine (Bamberger and Lodter, *Ber.*, 1887, **20**, 1703; Paal and Gerum, *Ber.*, 1909, **42**, 1553; Kirsanov and Ivastchenko, *Bull. Soc. chim.*, 1935, **2**, 1944). Introduction of naphthalene into the reaction mixture as an acceptor of nascent hydrogen (Bamberger and Lodter, *Annalen*, 1895, **288**, 74) led to only a slight increase in the yield.

Sodioaniline has hitherto been prepared from sodium and aniline at temperatures above 140°, usually in the presence of a catalyst (Belart, D.R.-P. 207,981; Deutsche Gold- und Silber-Scheide-Anstalt, D.R.-P. 215,339; Victoria, *Mem. Acad. Cienc. Artes Barcelona*, 1928, **21**, 227); in refluxing benzene the yield of sodioaniline (characterised as 2 : 4 : 6-tribromoaniline) was only 2%. Cessation of the reaction may be attributed to the formation of a protective coating on the powdered sodium in the absence of benzonitrile. The quantities of ionisable cyanide and amidine formed when equimolecular quantities of aniline, benzonitrile, and sodium were boiled in benzene excluded the possibility of the formation of sodioaniline by a mechanism similar to that postulated by Anker and Cook (*loc. cit.*) in the preparation of 1 : 2-dihydro-2 : 2 : 4 : 6-tetraphenyl-1 : 3 : 5-triazine from sodium and benzonitrile :

$$R{\cdot}CN + 2Na \longrightarrow RNa + NaCN$$
$$RNa + Ar{\cdot}NH_2 \longrightarrow Ar{\cdot}NH^-\}Na^+ + RH$$

Two other mechanisms for the main course of the reaction cannot be sustained. *N*-Arylamidine formation could be a consequence of the displacement of an equilibrium, set up between a nitrile, an arylamine, and an *N*-arylamidine, by conversion of the *N*-arylamidine into its insoluble sodio-derivative (cf. a similar equilibrium in the preparation of amidines and *N*-alkylamidines; Oxley, Partridge, and Short, *J.*, 1948, 303). *N*-Phenylbenzamidine does indeed react readily with powdered sodium in benzene to form its insoluble sodio-derivative, together with some benzylamine and aniline, but without the evolution of any permanent gas. However, no trace of *N*-phenylbenzamidine could be detected when aniline and benzonitrile were boiled together in benzene, and only a trace of *NN'*-diphenylbenzamidine was formed when these reagents were boiled together without solvent (cf. Oxley, Partridge, and Short, *loc. cit.*; Bernthsen, *Annalen*, 1877, **184**, 341; 1878, **192**, 4). The production of kyaphenin when benzonitrile is brought into reaction with sodium in boiling benzene (Hofmann, *Ber.*, 1868, **1**, 198; Lottermoser, *loc. cit.*) led us to examine the possibility of aminolysis of kyaphenin by aniline in the presence of sodium, but no amidine was detected.

The scope of the reaction when equimolecular quantities of a nitrile, an amine, and sodium or sodamide are employed, and its extension to the preparation of a benziminazole derivative, are illustrated by the examples described in the Experimental section. No amidine was obtained from *m*-nitrobenzonitrile, *p*-acetoxybenzonitrile, or *p*-nitroaniline. Some dehalogenation was observed in the preparation of *N*-*p*-chlorophenylbenzamidine. The formation of 2 : 4 : 5-triphenylglyoxaline as a by-product in the preparation of *N*-benzylbenzamidine may be accounted for as follows :



An alternative mechanism involving an addition of benzonitrile to sodio-*N*-benzylbenzamidine and subsequent cyclisation of the resultant sodio-diamidide by loss of ammonia

is rendered unlikely by the observation that no 2 : 4 : 5-triphenylglyoxaline could be isolated when sodio-*N*-benzylbenzamidine and benzonitrile were heated together. The formation of *p-sec.*-butoxy- (63%) and of *p*-benzyloxy-*N*-phenylbenzamidine (83%) is noteworthy, since these compounds could not be prepared by fusion of the appropriate nitriles with anilinium benzenesulphonate; by the fusion method, dealkylation occurred (cf. Sprung and Wallis, *J. Amer. Chem. Soc.*, 1934, **56**, 1715; Short and Stewart, *J.*, 1929, 553) and *p*-hydroxy-*N*-phenylbenzamidine was isolated in each case.

NN-Diaryl- and *N*-alkyl-*N*-aryl-amidines could not be prepared by this method. This may be related to a difference in stability of the carbazylate anions (Franklin, "The Nitrogen System of Compounds," New York, 1935); thus the anion derived from an *N*-arylamidine has a mesomeric structure, $R{\cdot}C(:NH){\cdot}\bar{N}Ar \longleftrightarrow R{\cdot}C(\cdot NH^-){:}NAr$, analogous to that of a carboxylate anion, whereas for the anion of an *NN*-disubstituted amidine only one similar structure can be written, $R{\cdot}C(:N^-){\cdot}NR'R''$. Stabilisation of the carbazylate anions of *N*-arylamidines may also provide an explanation of the failure of sodio-*N*-phenylbenzamidine to react with benzonitrile to form a diamidide or with bromobenzene to form *NN*- or *NN'*-diphenylbenzamidine.

An *N*-arylamidine is postulated by Hao-Tsing (*J. Amer. Chem. Soc.*, 1944, **66**, 1421) as an intermediate in the preparation of *p*-aminobenzaldehyde and *p*-aminoacetophenone by heating at 250—300° the product of interaction of aniline and hydrogen cyanide or acetonitrile respectively in the presence of hydrogen chloride. Spoerri and Du Bois ("Organic Reactions," New York, 1949, Vol. V, p. 396), however, consider these to be examples of the Hoesch reaction. We find that interaction of acetonitrile, aniline, and hydrogen chloride in dry ether at room temperature for a month affords *N*-phenylacetamidine in 90% yield; *N*-phenylbenzamidine (23%) was similarly prepared from benzonitrile. The thermal rearrangement of the *N*-arylamidinium chloride involved in the mechanism put forward by Hao-Tsing is analogous to the isomerisation of *N*-acylanilines to amino-ketones (Dippy and Wood, *J.*, 1949, 2719).

Experimental

Interaction of Aniline, p-Tolunitrile, and Sodium.—Aniline (10·1 g.), *p*-tolunitrile (25·4 g., 2 mols.), and powdered sodium (5 g., 2 atoms) were boiled together in dry, toluene-free benzene (100 c.c.) under reflux for 3 days. The mixture, when worked up essentially as described by Lottermoser (*loc. cit.*), afforded *N*-phenyl-*p*-toluamidine (0·95 mol.) and ionisable cyanide equivalent to 0·88 mol. of *p*-tolunitrile; in addition, toluene was characterised as benzoic acid (3·85 g., 0·15 mol.) by oxidation with potassium permanganate. In an oxidation of a similar artificial mixture containing toluene, benzoic acid was obtained in 49% yield.

N-Phenylbenzamidine.—(i) Aniline, benzonitrile (2 mols.), and sodium (2 atoms), on reaction as described above, gave *N*-phenylbenzamidine (0·96 mol.), ionisable cyanide equivalent to 0·88 mol. of benzonitrile, and kyaphenin (0·005 mol.).

(ii) Finely powdered sodamide (3·9 g.) and aniline (9·3 g., 1 mol.) were refluxed in benzene (100 c.c.) until most of the ammonia had been evolved (about 75 min.); benzonitrile (10·3 g., 1 mol.) was added, and the mixture boiled for a further 135 min. Basic material was extracted with hydrochloric acid and liberated by ammonia, whereby *N*-phenylbenzamidine (12·6 g., 64%), m. p. and mixed m. p. 114—115°, was obtained. With granular sodamide, the yield was 57%, and with dimethylaniline as solvent it was 23%.

(iii) A mixture of aniline (9·3 g.), benzonitrile (10·3 g., 1 mol.), and powdered sodium (2·3 g., 1 atom) in dry benzene (100 c.c.) was refluxed for 27 hours whilst connected to a gas burette; no permanent gas was evolved. After addition of ethanol (10 c.c.), ionisable cyanide was extracted with dilute sodium hydroxide and recovered as silver cyanide (0·73 g., 5·5%). Basic material was then collected in dilute hydrochloric acid, and *N*-phenylbenzamidine, m. p. and mixed m. p. 114—115°, was precipitated by sodium hydroxide. The alkaline filtrate was extracted with chloroform and from this, after concentration, an acetate-buffer extract (pH 4·5) afforded, on addition of sodium picrate, benzylammonium picrate (0·25 g.), m. p. 195—197°, not depressed on admixture with an authentic specimen (Found: N, 16·7. Calc. for $C_{13}H_{12}O_7N_4$: N, 16·65%). Benzaldehyde was isolated from the benzene liquors as its 2 : 4-dinitrophenylhydrazone (0·15 g.), m. p. and mixed m. p. 237—238°. With periods of heating of 6, 7, 15, and 23 hours, the yields of amidine were 68, 70, 69, and 76%, respectively; with

ether as solvent and 6 hours' heating, the yield was 32%. Addition of naphthalene (1 mol.) raised the yield to 81% but no 1 : 4-dihydronaphthalene could be isolated as its mercuric acetate complex.

Reaction between Aniline and Sodium.—When powdered sodium (2·3 g.) and aniline (9·3 g., 1 mol.) were refluxed in dry benzene (100 c.c.), the metal apparently underwent no change. The suspension was filtered. The residue was thoroughly washed with benzene and dissolved in ethanol and hydrochloric acid; after evaporation of the ethanol, addition of bromine afforded 2 : 4 : 6-tribromoaniline (0·7 g., 2%).

Reaction between N-Phenylbenzamidine and Sodium.—A suspension of sodium (1·15 g.) in a solution of *N*-phenylbenzamidine (9·8 g., 1 mol.) in dry benzene (150 c.c.) was refluxed in an apparatus connected to a gas burette until all the sodium had reacted (12 hours); no permanent gas was evolved. The suspended solid immediately dissolved on addition of hydrochloric acid; from the acid solution, *N*-phenylbenzamidine (7·75 g., 79%), benzylammonium picrate (1·4 g., 8%), and 2 : 4 : 6-tribromoaniline (2·05 g., 12%) were obtained as indicated above.

Interaction of Aniline and Benzonitrile.—(i) A mixture of aniline (18·6 g.) and benzonitrile (20·6 g., 1 mol.) was boiled for 8 hours, and material volatile at 100°/10 mm. distilled off. A lactic acid extract of the residue afforded with sodium picrate, *NN'*-diphenylbenzamidinium picrate (0·2 g.), m. p. and mixed m. p. 216° (Found: N, 14·0. Calc. for $C_{25}H_{19}O_7N_5$: N, 13·95%). (ii) Repetition of the foregoing experiment but with benzene as solvent and 3 days' heating yielded no material not volatile at 100°/10 mm. giving a water-insoluble base or picrate. (iii) *N*-Phenylbenzamidine when heated at 183° for 24 hours yielded aniline (24%) (characterised as 2 : 4 : 6-tribromoaniline), benzonitrile (20%) (characterised as *m*-nitrobenzonitrile), and *NN'*-diphenylbenzamidine (19%); no unchanged *N*-phenylbenzamidine was detected.

Attempted Aminolysis of Kyaphenin.—From the mixture obtained after refluxing kyaphenin (10·3 g.), sodium (2·3 g., 3 atoms), and aniline (9·3 g., 3 mols.) in dry benzene (100 c.c.) for 29 hours, kyaphenin (9·3 g., 90%) was recovered unchanged.

General Methods.—The results of experiments involving two general methods (A and B) for the preparation of *N*-substituted amidines are summarised in the Table. Further details are given below of cases which involved special features.

A. Powdered sodium (2·3 g.), the amine (0·1 mol.), and the nitrile (0·1 mol.) were refluxed in dry benzene (100 c.c.) with a soda–lime guard-tube for 20—30 hours. Ethanol (15 c.c.) was added to dissolve any unchanged sodium and to decompose the sodioamidine. The base was collected in aqueous lactic acid; after charcoal treatment, it was recovered by addition of ammonia and crystallised, usually from light petroleum (b. p. 100—120°).

B. Granular sodamide (4·3 g.), the amine (0·1 mol.), and the nitrile (0·1 mol.) were used in a procedure which was otherwise identical with method A.

N-p-*Chlorophenylbenzamidine.*—Interaction of benzonitrile, *p*-chloroaniline, and sodium for 2 days by method A afforded crude basic material (12·7 g.), m. p. 83—91°. This on treatment with hydrochloric acid yielded N-p-*chlorophenylbenzamidinium chloride dihydrate* (12·8 g., 42%), which crystallised as needles, m. p. 103—106° (efferv.), from water (Found: loss at 50°/2 mm., 11·65. Found, on dried material: N, 10·75. $C_{13}H_{12}N_2Cl_2,2H_2O$ requires H_2O, 11·9%. $C_{13}H_{12}N_2Cl_2$ requires N, 10·5%); von Walther (*J. pr. Chem.*, 1903, **67**, 450) records m. p. 103—108° (decomp.) but no analyses. The *acetate* crystallised as needles, m. p. 131—132°, from benzene (Found: N, 10·0. $C_{15}H_{15}O_2N_2Cl$ requires N, 9·65%). The base had m. p. 114—115°, depressed to below 100° by *N*-phenylbenzamidine (Found: N, 12·4. Calc. for $C_{13}H_{11}N_2Cl$: N, 12·15%), and the picrate had m. p. 180—181°; Oxley and Short (*J.*, 1949, 453) state that the amidine and its picrate have m. p. 117° and 183°, respectively. The mother-liquor from the crystallisation of the chloride was basified, and the precipitate afforded on crystallisation from light petroleum (b. p. 100—120°) *N*-phenylbenzamidine (0·4 g.), m. p. and mixed m. p. 114—116°, depressed to 83—93° by *N*-*p*-chlorophenylbenzamidine.

N-*Benzylbenzamidine.*—The base, obtained after interaction of benzylamine, benzonitrile, and sodium by method A, on treatment with hydrochloric acid yielded *N*-benzylbenzamidinium chloride (7·6 g., 31%), m. p. and mixed m. p. 226—228° after crystallisation from *iso*propanol. The free base had m. p. 77·5—78·5°; Pyman (*J.*, 1923, **123**, 3373) records m. p. 77—78°. The solid (2·3 g., m. p. 276—278°) which separated during extraction of the base was crystallised from ethanol and afforded 2 : 4 : 5-triphenylglyoxaline (1·55 g.), m. p. 280—281°, undepressed on admixture with an authentic specimen.

When equimolecular quantities of *N*-benzylbenzamidine, benzonitrile, and sodium were boiled together in benzene for 24 hours no 2 : 4 : 5-triphenylglyoxaline could be detected amongst the products; *N*-benzylbenzamidine (89%) and a trace of kyaphenin were recovered.

N-2-*Hydroxyethylbenzamidine*.—Ethanolamine, benzonitrile, and sodium, brought into reaction by method A, afforded kyaphenin (0·55 g.) and a mixture of bases which was converted into the mixed picrates (4·4 g.); by fractional crystallisation from ethanol, these were separated into benzamidinium picrate (1·25 g., 4%), m. p. and mixed m. p. 237—238°, and N-2-*hydroxy-*

No.	Compound	Method	Yield, %	M. p.	Formula	Found: N, %	Reqd.: N, %
1	*N*-Phenyl-*p*-toluamidine	A	65	151—152°	—	—	—
2	*N*-Phenyl-*p*-anisamidine	A	51	147—148	—	—	—
3	p-*Chloro*-N-*phenylbenzamidine*	A	64	140—141	$C_{13}H_{11}N_2Cl$	12·3	12·15
4	p-sec.-*Butoxy*-N-*phenylbenzamidine*	A	63	116—116·5	$C_{17}H_{20}ON_2$	10·5	10·45
5	*N*-*o*-Tolylbenzamidine	A	61	109—110	$C_{14}H_{14}N_2$	13·3	13·3
6	*N*-*p*-Methoxyphenylbenzamidine	A	73	115·5—116·5	$C_{14}H_{14}ON_2$	12·3	12·4
7	N-2-*Naphthylbenzamidine*	A	39	128·5—129·5	$C_{17}H_{14}N_2$	11·2	11·4
		B	54	—	—	11·4	—
8	*N*-2-Pyridylbenzamidine	A	65	98·5—99·5	$C_{12}H_{11}N_3$	21·0	21·3
9	*N*-*cyclo*Hexylbenzamidine	A	43	115—116	$C_{13}H_{18}N_2$	14·1	13·85
10	*N*-Phenyl-*o*-toluamidine	B	47	122—123	$C_{14}H_{14}N_2$	13·4	13·3
11	p-*Benzyloxy*-N-*phenylbenzamidine*	B	83	183·5—184·5	$C_{20}H_{18}ON_2$	9·45	9·25
12	N-2-*Thiazolylbenzamidine*	B	6	90—91	$C_{10}H_9N_3S$	20·9	20·65
13	*N*-Phenylphenylacetamidine	B	64	140—141	$C_{14}H_{14}N_2$	13·3	13·3
14	*N*-Phenylacetamidine	B	36	—	—	—	—
15	2-Phenylbenziminazole	B	72	299—301	$C_{13}H_{10}N_2$	14·4	14·45

Picrate of No.	M. p.	Formula	Found: N, %	Reqd.: N, %
1	152—153°	—	—	—
2	129—130	$C_{20}H_{17}O_8N_5$	15·2	15·4
3	175—176	$C_{19}H_{14}O_7N_5Cl$	15·5	15·25
4	138—140	$C_{23}H_{23}O_8N_5$	14·3	14·1
5	152—153	$C_{20}H_{17}O_7N_5$	15·5	15·95
6	171—173	—	—	—
7	216·5—218	$C_{23}H_{17}O_7N_5$	14·9	14·75
8	206—207	—	—	—
9	142—143	$C_{19}H_{21}O_7N_5$	16·5	16·25
10	175—176	$C_{20}H_{17}O_7N_5$	15·9	15·95
11	145—146	$C_{26}H_{21}O_8N_5$	13·3	13·2
12	162—163	$C_{16}H_{12}O_7N_6S$	18·9	19·45
13	109—110	$C_{20}H_{17}O_7N_5$	15·8	15·95
14	190—191	$C_{14}H_{13}O_7N_5$	19·05	19·25
15	275—276 (decomp.)	$C_{19}H_{13}O_7N_5$	16·8	16·55

Notes.—1 and 2, Admixture with authentic specimens (Oxley and Short, *J.*, 1949, 453; Hullin, Miller, and Short, *J.*, 1947, 394) caused no depression of the m. p. of these bases. Oxley and Short (*loc. cit.*) record m. p. 153° for *N*-phenyl-*p*-toluamidinium picrate. 4, The reaction was exothermic and was initiated without heating. 5, Lottermoser (*loc. cit.*) records m. p. 105—108° for this amidine. 6, The base and picrate exhibited no depression of m. p. on admixture with authentic specimens (Oxley and Short, *loc. cit.*). 7, The period of heating in method B was 80 hours. The base crystallised from light petroleum (b. p. 100—120°) as colourless rods, m. p. 128·5—129·5°, whereas from aqueous ethanol, it afforded pale yellow plates, m. p. 122—123°; neither of the two forms was solvated and they were readily interconverted by crystallisation from the appropriate solvent. This compound was also prepared in 75% yield by interaction in the usual way (Oxley, Partridge, and Short, *J.*, 1947, 1110) of equimolecular quantities of benzonitrile, β-naphthylamine, and aluminium chloride at 180—190° for 30 minutes; its *hydrochloride* crystallised as prisms, m. p. 250·5—251°, from dilute hydrochloric acid (Found: N, 10·1. $C_{17}H_{15}N_2Cl$ requires N, 9·9%). 8, Authentic specimens (Oxley, Partridge, and Short, *J.*, 1947, 1115) did not depress the m. p.s of the base and its picrate. 9, The period of heating was 2 days; Oxley and Short (*loc. cit.*) record m. p. 116—116·5° for the base and m. p. 143° for the picrate. 10, Lottermoser (*loc. cit.*) records m. p. 121—123° for this base. 12, The m. p. of the base was depressed to below 80° on addition of 2-aminothiazole (Found, for the picrate: C, 44·6; H, 3·2. Reqd.: C, 44·45; H, 2·8%). 13, Before the addition of the phenylacetonitrile, the aniline and sodamide were refluxed in the benzene for 30 minutes. 14, The reaction was conducted as described for example 13, but the second period of heating was reduced to 7 hours and the product was isolated as the picrate. 15, Heating was for 6 hours.

ethylbenzamidinium picrate (2·15 g., 6%) which crystallised as prisms, m. p. 140—142°, with resolidification and melting again at 180—215° (decomp.) (Found: C, 46·0; H, 3·95; N, 17·6. $C_{15}H_{15}O_8N_5$ requires C, 45·8; H, 3·85; N, 17·8%).

p-sec.-*Butoxybenzonitrile*, prepared in 53% yield from *sec.*-butyl bromide, *p*-cyanophenol, and sodium ethoxide (Partridge, *J.*, 1949, 3043), had b. p. 109—111°/1·3 mm., n_D^{20} 1·5256 (Found: N, 8·0. $C_{11}H_{13}ON$ requires N, 8·0%).

p-sec.-*Butoxybenzonitrile and Anilinium Benzenesulphonate*.—There was considerable effervescence when this nitrile (16·4 g.) and the salt (23·5 g., 1 mol.) were heated at 210° for

75 minutes. A solution of the product in hot water, on cooling, deposited *p*-hydroxy-*N*-phenylbenzamidinium benzenesulphonate (21·7 g., 63%), m. p. 180—182°, not depressed on admixture with an authentic specimen. The mother-liquors afforded no alkali-insoluble base on the addition of sodium hydroxide. p-*Hydroxy*-N-*phenylbenzamidinium picrate* crystallised from aqueous *iso*propanol as prisms, m. p. 82—84° (Found: loss at 60°/1 mm., 7·1. Found, on dried material: N, 16·05. $C_{19}H_{15}O_8N_5,2H_2O$ requires H_2O, 7·55%. $C_{19}H_{15}O_8N_5$ requires N, 15·85%). The *base*, liberated by sodium hydrogen carbonate, crystallised from *iso*propanol as clusters of small needles, m. p. 182·5—183° (Found: N, 13·0. $C_{13}H_{12}ON_2$ requires N, 13·2%).

p-*Benzyloxybenzonitrile and Anilinium Benzenesulphonate.*—Equimolecular quantities of these reagents reacted exothermally when heated at 210° for 90 minutes; from the melt only *p*-hydroxy-*N*-phenylbenzamidine could be isolated as its picrate (3·4 g., 12%).

p-*Acetoxybenzonitrile and Anilinium Benzenesulphonate.*—The basic fraction of an aqueous extract of the melt obtained by heating the nitrile (8·05 g.) and the aniline salt (12·6 g., 1 mol.) at 210° for 1 hour consisted of *NN'*-diphenylacetamidine (1·2 g.) and *N*-phenylacetamidine [picrate (1·35 g.), m. p. and mixed m. p. 188—189°]. Since all the substances used in this experiment were dry, it is possible that *N*-phenylacetamidine was formed from the *p*-acetoxybenzonitrile:

$$3Ph\cdot NH_3^+ + 2CH_3\cdot CO_2\cdot C_6H_4\cdot CN + Ph\cdot SO_3^- \longrightarrow CH_3\cdot C(:NHPh^+)\cdot NHPh + CH_3\cdot C(:NH_2^+)\cdot NHPh + HO\cdot C_6H_4\cdot CN + HO\cdot C_6H_4\cdot CO_2H + Ph\cdot SO_3H$$

In agreement with this, phenyl acetate and anilinium benzenesulphonate, brought into reaction under the same conditions, afforded as basic product only *NN'*-diphenylacetamidine (3%).

Interaction of Nitriles, Aniline, and Hydrogen Chloride.—(i) A solution of aniline (9·3 g.) in dry ether (50 c.c.) was saturated with dry hydrogen chloride, acetonitrile (8·2 g.; 2 mols.) added, and the mixture kept at room temperature for a month; the anilinium chloride slowly dissolved and a viscous oil separated. The solvent was evaporated, and the residue dissolved in water and diluted to 250 c.c. *N*-Phenylacetamidinium picrate (3·2 g., 9%), m. p. and mixed m. p. 191—192°, was precipitated from an aliquot (25 c.c.). The base was liberated from the remainder, collected in chloroform, dried (K_2CO_3), and recovered (yield 11 g., 82%, m. p. 55—63°). On recrystallisation from light petroleum (b. p. 60—80°), it crystallised as needles, m. p. 70—71° (Found: N, 21·0. Calc. for $C_8H_{10}N_2$: N, 20·9%). Bernthsen (*Annalen*, 1877, **184**, 358) describes this compound as an oil.

(ii) Benzonitrile under the same conditions afforded *N*-phenylbenzamidine in 23% yield.

THE UNIVERSITY, NOTTINGHAM. [*Received, September 26th*, 1952.]

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53. *The Reaction of Ring-substituted* cyclo*Hexylamines with Nitrous Acid. An Interpretation based on Conformational Analysis.*

By J. A. MILLS

Deamination of *cyclo*hexylamines with simple alkyl substituents in the ring is conformationally specific: equatorial amino-groups afford alcohols of the same configuration; polar amino-groups react by elimination plus inversion. The retention of configuration in the deamination of equatorial amino-groups is a true stereospecific process, and a pyramidal transition state is postulated to explain this. The principles of conformational analysis are used to assign configurations to *cis*-decalyl derivatives.

SIMPLE acyclic primary amines not containing reactive neighbouring groups undergo deamination through intermediate formation of a diazonium ion which decomposes by a S_N1 process and affords an alcohol of largely inverted configuration, *e.g.*:

$$L\text{-}R\cdot NH_2 + HNO_2 \longrightarrow R\cdot N_2^+ \longrightarrow R^+ \longrightarrow D\text{-}R\cdot OH + DL\text{-}R\cdot OH$$

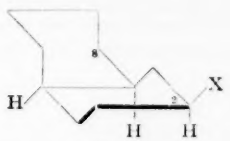
(Brewster, Hiron, Hughes, Ingold, and Rao, *Nature*, 1950, **166**, 179). Kinetic studies have not been made on simple cyclic primary amines, but Hückel's summary of his own work and that of others (*Annalen*, 1938, **533**, 1) and a recent publication by Cornubert (*Bull. Soc. chim.*, 1951, C 23) show that the deamination of primary *cyclo*hexylamines with simple alkyl substituents in the ring does not follow the simple pattern of the acyclic amines. Of an

epimeric pair of amines, it is usual for one epimer (*e.g.*, menthylamine, carvomenthylamine, *iso*menthylamine) to give on deamination a good yield of alcohol of predominantly the same configuration as the amine used, whereas the other (*neo*menthylamine, *neo*carvomenthylamine, etc.) undergoes much elimination, but may afford some alcohol of largely inverted configuration. This also holds for epimeric amino-*trans*-decalins (Hückel, *loc. cit.*), but, following recent configurational assignments by Dauben and Hoerger (*J. Amer. Chem. Soc.*, 1951, **73**, 1504), it is probable that *all four* possible 1- and 2-amino-*cis*-decalins are deaminated with retention of configuration. In the *cyclo*pentane series, both the epimeric 2-*cyclo*pentyl*cyclo*pentylamines are deaminated with elimination plus inversion (Hückel, Gross, and Doll, *Rec. Trav. chim.*, 1938, **57**, 555).

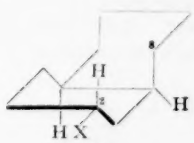
Only in the *cyclo*hexane series has the peculiar difference between epimers been observed, and to understand the cause it is necessary to apply modern ideas on the stereochemistry of *cyclo*hexane derivatives. All of the *cyclo*hexylamines named may exist with the ring in its more stable, " chair " conformation, and the amino-groups will then occupy either " equatorial " (*e*) or " polar " (*p*) positions. The factors deciding the most stable conformation of a particular substance have been discussed by Hassel and Ottar (*Acta Chem. Scand.*, 1947, **1**, 929), Beckett, Pitzer, and Spitzer (*J. Amer. Chem. Soc.*, 1947, **69**, 2488), Barton (*Experientia*, 1950, **6**, 316), Johnson (*ibid.*, 1951, **7**, 315), and Barton and Rosenfelder (*J.*, 1951, 1048).

First, it may be deduced that the course of deamination of *cyclo*hexylamines is conformationally specific; if the amino-group is equatorial in the most stable conformation of the molecule, deamination affords an alcohol of the same configuration; if it is polar, elimination and inversion occur. For the monocyclic amines this is easily demonstrated; Barton (*loc. cit.*) has assigned conformations to some of them, and the same principles apply to the others. Barton has also discussed general relations between conformation, reactivity, stability, and mode of formation, and when these are applied to the data collected by Hückel configurations and conformations are readily derived for ***trans***-decalin derivatives; the 1- and the 2-amino-*trans*-decalin with equatorial amino-groups afford on deamination *trans*-decalols of the same configuration, whereas their epimers with polar amino-groups react by elimination plus inversion.

The reason why all 1- and 2-amino-*cis*-decalins are deaminated with retention of configuration is that a single substituent at positions other than ring junctions in *cis*-decalin tends to occupy an equatorial position. This gives the maximum number of *e* substituents, and is possible because of the flexibility of the accepted conformation of *cis*-decalin (Bastiansen and Hassel, *Nature*, 1946, **157**, 765) which may exist in two equivalent forms, interconvertible by transforming all *e* bonds into *p* and *vice versa*. (I) and (II) show the more stable conformations of an epimeric pair of *cis*-2-decalyl derivatives, each with the substituent X equatorial. This flexibility of *cis*-decalin is reduced if more than one substituent is present.



(I)



(II)

Secondly, it may be deduced that the retention of configuration observed in deamination of equatorial amino-groups is due to a stereospecific process. For monocyclic amines such as menthylamine, one epimer of which has an *e* and the other a *p* amino-group, the retention of configuration during deamination of the *e* epimer may be due to a stereospecific process, or may merely follow from hydroxylation of some intermediate by a mechanism which gives an alcohol with the most stable conformation. The almost complete retention of configuration proved by Dauben and Hoerger (*loc. cit.*) to occur during deamination of both epimeric 2-amino-*cis*-decalins is decisive: configuration must be retained at every stage during deamination of equatorial amino-groups.

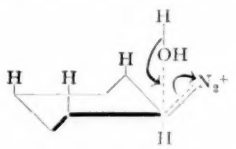
This evidence excludes a true carbonium ion as intermediate, because the distinction between the epimeric amines would disappear at that stage, and each would give rise to the same mixture of the two possible equatorial alcohols if maximum stability were the only requirement for the hydroxylation process. In any case, a mechanism involving carbonium ions would have been unlikely in deaminations with retention of configuration, because with, *e.g.*, menthylamine those molecular rearrangements which should result from the presence of a positive charge adjacent to a methine group (Wallis, in Gilman's "Organic Chemistry," Wiley, New York, 2nd edn., 1943, vol. I, pp. 1004—1009; Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173) seem to be absent.

There is no reason to doubt the formation of a diazonium ion as an intermediate in all deaminations; it is in the mode of its decomposition that the *cyclo*hexylamines differ from saturated acyclic amines. All published deaminations have been carried out in acid solution, and must involve attack on the diazonium ion by a water molecule, not a hydroxyl ion. The only requirement is that the acidity should not be so high as to prevent the formation of the diazonium ion (Kornblum and Iffland, *J. Amer. Chem. Soc.*, 1949, **71**, 2137). Successful deaminations are possible in very weakly acidic solutions, *e.g.*, Wallach (*Annalen*, 1907, **353**, 318) noted that a few drops of acetic acid suffice for the decomposition of aqueous solutions of menthylamine nitrite. In the following discussion will be found suggestions that both elimination and displacement with retention are bimolecular processes, but as usually carried out they will have first-order kinetics. It seems impossible to apply the decisive test of carrying out the decomposition of the diazonium ion in the presence of base, because of the great speed of the second stage of the reaction, and the necessity for acidic conditions in the first stage.

Barton and Rosenfelder (*loc. cit.*) have shown that steroid vicinal dibromides suffer easy elimination in the presence of iodide ion only if the atoms eliminated are *trans* and both polar, so that four atomic centres are coplanar (cf. Winstein, Pressman, and Young, *J. Amer. Chem. Soc.*, 1939, **61**, 1645). They pointed out that a similar geometric specificity seems to hold for other elimination reactions of *cyclo*hexane derivatives, including that resulting from the action of nitrous acid on *cyclo*hexylamines. If the regular occurrence of elimination with amines containing polar amino-groups is due to the presence of an adjoining polar (*trans*) hydrogen atom, the reaction may proceed by the path shown in (III).

This representation of the reaction as an $E2$ process, rather than as the $E1$ elimination observed for acyclic amines, encounters some difficulties. From the data of Hückel, Tappe, and Legutke (*Annalen*, 1940, **543**, 191) it is seen that, when alternative paths for *trans*-elimination are available, elimination towards a methine group is always prominent, and may predominate, whereas Dhar, Hughes, Ingold, Mandour, Maw, and Woolf (*J.*, 1948, 2093) have shown that base-induced $E2$ elimination from other 'onium ions follows the Hofmann rule of preferential elimination away from a methine group if possible. However, the extent of elimination towards a methine group during deamination of polar amino-groups is not as great as that during solvolysis ($E1$) reactions of related halides and toluene-*p*-sulphonates. Although the observed elimination of polar amino-groups may not yet be fully explicable, the postulate of the transition state shown in (III) seems to provide a

(III)

 (IV)

valid criterion for studies on configuration. Carbonium ions evidently play some part in the reaction, as *neo*menthylamine affords some menthan-4-ol and traces of menthol (Hückel, Tappe, and Legutke, *loc. cit.*); the menthol may arise by the mechanism which holds for the deamination of acylic amines.

For the deamination of *cyclo*hexylamines with equatorial amino-groups, the simplest mechanism which accommodates the facts is shown in (IV). A broadside displacement of the diazonium group by a water molecule, proceeding through a pyramidal transition state,

will be a stereospecific process resulting in retention of configuration. The geometry of the chair ring is favourable to this type of displacement when the group to be displaced is equatorial, and at the same time unfavourable to either displacement with inversion or *trans*-elimination.

There are certain theoretical objections to a pyramidal transition state in displacement reactions (Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1252), and more decisive evidence is needed; as stated above, the kinetic approach is likely to be difficult. It may be noted that one example of deamination of a primary amine to an alcohol with retention of configuration, under conditions where intermediate formation of a carbonium ion is improbable, is provided by 1-amino*apo*camphane (Bartlett and Knox, *J. Amer. Chem. Soc.*, 1939, **61**, 3184); in this, the environment of the bridge-head amino-group is in some respects comparable to that of an equatorial amino-group in simple *cyclo*hexylamines.

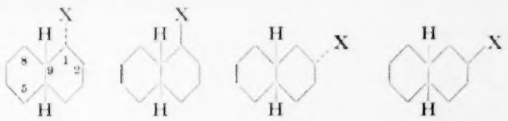
The deamination of *cyclo*hexylamines containing reactive neighbouring groups is not considered here; the dependence of the course of deamination on geometric factors has been discussed for the 2-hydroxy*cyclo*hexylamines by McCasland (*ibid.*, 1951, **73**, 2293).

In our opinion, it may be assumed as a working hypothesis that the deamination of a purely equatorial amino-group would occur with complete retention of configuration and without elimination, and that the existence of partial polar character in the amino-group is indicated if some elimination and partial inversion occur. The concept of a purely equatorial amino-group cannot at present be illustrated by examples, but the hypothesis is in harmony with published data. Menthylamine, the 1-amino-*trans*-decalin with an acetyl derivative of m. p. 141°, and the 2-amino-*trans*-decalin with an acetyl derivative of m. p. 88°, which appear to show complete retention and no elimination on deamination (Hückel, *loc. cit.*), have a strong tendency to exist in conformations with *e*-amino-groups because all substituents will then be *e*. The extent of elimination appears to increase in the order, carvomenthylamine, *iso*menthylamine, *iso*carvomenthylamine (cf. Hückel, *loc. cit.*, and refs. cited there), which conformational analysis indicates to be the order of increasingly polar character in the amino-group, although on balance this group still will be equatorial.

We have used the concepts developed above, with other established principles of conformational analysis, in attempts to check the assigned configurations of amines and alcohols of the *cis*-decalin series. The Table sets out the experimental data (Hückel, *loc. cit.*; Hückel, Tappe, and Legutke, *loc. cit.*; Hückel, *Ber.*, 1934, **67**, *A*, 129), and the suggested configurations. Dauben and Hoerger (*loc. cit.*) established the amine–alcohol relations for the 2-substituted compounds, and on the basis of catalytic hydrogenation data suggested the relative configurations (VII) and (VIII). The following argument strongly supports these assignments.

cis-*Decalylamines and* cis-*Decalols*

(Experimental data relate to the racemic substances corresponding to the active forms shown. The percentages are the approximate figures quoted by Hückel.)



	(V)	(VI)	(VII)	(VIII)
Alcohols (X = OH).				
M. p.	93°	55°	105°	18 or 31°
Amount of epimer present after equiln., %	*	*	80	20
Rate of hydrolysis (60°) of:				
hydrogen phthalate	0·0635	0·0209	—	—
hydrogen succinate	—	—	3·207	2·113
Amines (X = NH_2).				
M. p. of acetyl deriv.	181°	141°	88°	153
Elimn. during deamin., %	0	25	0	30
Retention during deamin., %	100	90	100	90

* Not measurable.

Complete inversion of the conformation (II) which we believe to be the most stable for a substance of configuration (VIII) brings the functional group into a polar position, and in effect converts a conformation with three *e* and two *p* into one with three *p* and two *e* groups; the difference in stability between the conformation (II) and the inverted conformation may not be very great, and the existence of a certain proportion of molecules with a polar amino-group is to be expected for (VIII; X = NH_2). For a substance with configuration (VII), inversion of the most probable conformation (I) causes the same alteration in the numbers of *e* and *p* groups, but when the functional group is *p* the $C_{(8)}$-group is also *p* and on the same side of the ring to which the two groups are attached; such an arrangement causes a marked overlapping of van der Waals barriers of individual atoms, and is likely to be associated with conformational instability (Hassel and Ottar, *loc. cit.*); therefore the structure (VII) should have much less tendency than (VIII) has to exist with the functional group polar. The greater reactivity and greater stability of the alcohol (VII; X = OH) relative to its epimer, and the more complete retention and absence of elimination during deamination of the amine (VII; X = NH_2), agree with the deduction that equatorial character should be more marked in the functional group of these substances than in their epimers. In these cases the examination of static models is misleading.

Similar reasoning supports the configurations (V) and (VI) for the *cis*-1-decalyl derivatives shown in the Table, which are the original assignments deduced by Hückel (*locc. cit.*) from the methods of preparation. In (V) the functional group is unlikely to take up the polar position because of the resulting interference from the $C_{(5)}$-group. In this series two items of supporting evidence are available. Barton (*J.*, 1949, 2174) has pointed out that, since in the Tschugaev elimination reaction the *cis*-decal-1-ol of m. p. 93° undergoes elimination preferentially towards $C_{(2)}$ (Hückel, Tappe, and Legutke, *loc. cit.*), the hydroxyl group in this alcohol must be *trans* to the $C_{(9)}$-H, because *cis*-elimination is the rule in the Tschugaev reaction (cf. also Alexander and Mudrak, *J. Amer. Chem. Soc.*, 1950, **72**, 1810) and occurs preferentially towards a methine group if possible. The hydrocarbon formed during deamination of the 1-amino-*cis*-decalin with the acetyl derivative of m. p. 141° is principally Δ^1-*cis*-octalin (Hückel, Tappe, and Legutke, *loc. cit.*), which is evidence for a *cis*-relation between the amino-group and the $C_{(9)}$-H, suppressing the otherwise preferred elimination towards the methine group.

If these configurational assignments are correct, the absence of elimination between the *trans*-amino-group and $C_{(9)}$-H in (V) is noteworthy; indeed, these *cis*-decalin derivatives provide some of the most striking examples of conformational influence on reactivity so far recognised.

It is possible that certain *cis*-decalin derivatives may have conformations different from the possible ones mentioned above, *e.g.*, one chair ring and one boat ring. In the absence of a stabilising factor, such as a bridge, all of these other conformations appear to be less probable than the two-chair types discussed, and in most cases would support the view that configuration (V) should have more equatorial character than (VI), and (VII) more than (VIII).

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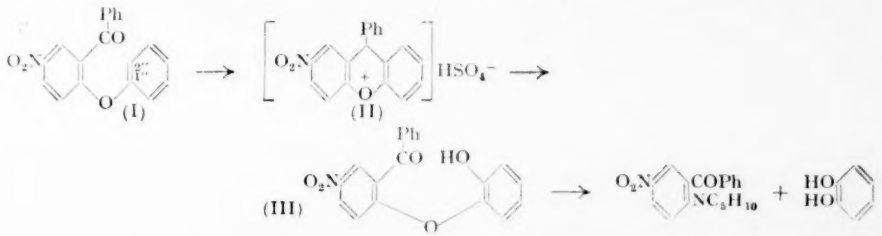
University Chemical Laboratory, Cambridge. [*Received, October 1st*, 1952.]

54. ortho-*Hydroxylation of Phenols. Part II.* Derivatives of Catechol.*

By J. D. Loudon and J. A. Scott.

In development of work described in Part I * a number of homologues of phenol have been converted into their catechol or guaiacol analogues through intermediates of the 2-aryloxy- and 2-(2-hydroxy-aryloxy)-5-nitrobenzophenone types. In certain intermediates of the latter class further examples of the Smiles rearrangement have been noted.

In a preliminary survey, now regarded as Part I,* the practicability of a new method of preparing catechols from phenols was established for a few simple cases. The method consists of three practical steps exemplified by (*a*) conversion of the phenol into an aryloxynitrobenzophenone of type (I), (*b*) hydroxylation of (I) to (III) through the intermediate but unisolated xanthylium sulphate (II), and (*c*) scission of (III) by piperidine, thereby liberating the catechol. Inclusion of an alkylation step, prior to scission, leads to monoalkyl ethers of catechols. The whole process is simple, rapidly carried out, and suitable for preparations on the small scale. Its extension to certain derivatives of pyrogallol, through renewed hydroxylation at stage (III), is discussed in the following paper. Meanwhile a more comprehensive study has been made of the method in its application to homologues of phenol. This was primarily designed to discover optimum conditions for the critical hydroxylation step in this class of compound, but incidentally minor improvements were made in other phases of the process (see Experimental).



The 2-aryloxy-5-nitrobenzophenones of type (I), listed in Table 1, were prepared in satisfactory yield from the appropriate phenols by reaction with 2-chloro-5-nitrobenzophenone. Hydroxylation was effected by dissolving the compound in concentrated sulphuric acid, diluting the solution with acetic acid, and adding hydrogen peroxide. Of the variables examined the ultimate concentration of sulphuric acid appears to be the most significant and the least easy to standardise. It must be sufficiently high to prevent the precipitation of colourless peroxides (Part I, *loc. cit.*) and yet low enough to avoid the formation of red by-products. The tendency to form these coloured by-products was troublesome only in hydroxylating the compounds (VIII), (IX), and (X) where a relatively low concentration of sulphuric acid was advantageous. Otherwise the hydroxylated products, listed in Table 2, were prepared under uniform conditions, the yield in all cases being high although those compounds in which a substituent is present in position 6, *viz.*, (XIV), (XV), and (XXI), proved difficult to crystallise. An interesting variation was observed in the colour of the compounds of type (III). In general it ranged from pale to bright yellow but two compounds, *viz.*, (XVII) and (XXII), were obtained colourless. In both cases, however, there was also evidence of a yellow form: thus the colourless form of (XVII) afforded a yellow solution in ethanol and, in the case of (XXII), the colourless variety was interconvertible, through crystallisation, with a yellow form. Possibly chromoisomerism is more general in this class of compound than has so far been detected.

* *J.*, 1950, 55, is regarded as Part I.

It was previously shown (Part I, *loc. cit.*) that in presence of alkali the benzoylated nitrophenyl group of compounds of type (III) may migrate from one to the other oxygen atom when the phenolic ring is unsymmetrically substituted. Such rearrangement renders ambiguous the structures of *O*-alkylation products prepared in presence of alkali but it

TABLE 1. *2-Aryloxy-5-nitrobenzophenones.*

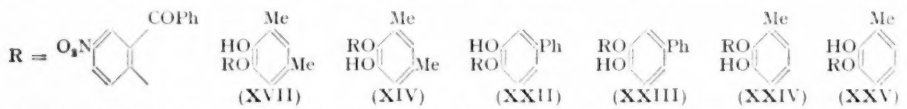
No.	Subst.	M. p.	Formula	Found, % C	Found, % H	Required, % C	Required, % H
IV	2″ : 4″-Me_2	109°	$C_{21}H_{17}O_4N$	72·7	5·0		
V	2″ : 5″-Me_2	120	,,	72·7	5·0	72·6	4·9
VI	3″ : 4″-Me_2	133	,,	72·7	4·9		
VII	3″ : 5″-Me_2	117·5	,,	72·45	4·8		
VIII	4″-Pr^i	82	$C_{22}H_{19}O_4N$	73·0	5·4	73·1	5·3
IX	4″-Bu^t	85	$C_{23}H_{21}O_4N$	73·75	5·7	73·6	5·6
X	4″-CMe_2·CH_2Bu^t	117	$C_{27}H_{29}O_4N$	75·2	7·1	75·1	6·8
XI	2″-Ph	97—98	$C_{25}H_{17}O_4N$	75·9	4·4		
XII	3″-Ph	58—60	,,	76·1	4·45	76·0	4·3
XIII	4″-Ph	126	,,	76·2	4·35		

TABLE 2. *2-(2″-Hydroxyaryloxy)-5-nitrobenzophenones.*

No.	Subst.	Source	M. p.	Formula	Found, % C	Found, % H	Required, % C	Required, % H
XIV	4″ : 6″-Me_2	IV	108°	$C_{21}H_{17}O_5N$	69·6	4·8		
XV	3″ : 6″-Me_2	V	132	,,	69·6	4·6	69·4	4·7
XVI	4″ : 5″-Me_2	VI	166	,,	69·5	5·0		
XVII	3″ : 5″-Me_2	VII	166	,,	69·35	4·6		
XVIII	4″-Pr^i	VIII	75	$C_{22}H_{19}O_5N$	70·3	5·05	70·0	5·1
XIX	4″-Bu^t	IX	115	$C_{23}H_{21}O_5N$	70·45	5·2	70·6	5·4
XX	4″-CMe_2·CH_2Bu^t	X	145	$C_{27}H_{29}O_5N$	72·5	6·7	72·5	6·5
XXI	6″-Ph	XI	141	$C_{25}H_{17}O_5N$	72·8	4·0		
XXII	5″-Ph	XII	144 [a]	,,	73·1	4·3	73·0	4·2
		XII	125 [b]	,,	72·8	4·2		
XXIII	4″-Ph	XIII	119	,,	73·1	4·0		

[a] Colourless. [b] Yellow.

is not encountered in methylations effected by diazomethane. Further experience has confirmed the view that rearrangement is seldom complete and presumably reaches an equilibrium position which is individually determined. When either (XVII) or (XIV) was dissolved in alkali subsequent acidification afforded in each case a substance which was readily identified as slightly impure (XIV). Likewise methylation of (XVII) or (XIV) by means of methyl sulphate and alkali afforded the methyl ether (XIV*a*) of the latter compound. By the action of diazomethane the same methyl ether was obtained from (XIV),



(**XVII**) (**XIV**) (**XXII**) (**XXIII**) (**XXIV**) (**XXV**)

(**XVII***a*; MeO for HO) (XIV*a*; MeO for HO) (XXII*a*; MeO for HO) (XXIII*a*; MeO for HO)

whereas (XVII) gave the different methyl ether (XVII*a*). In this case, (XIV) clearly predominates over (XVII) in alkaline solution and a similar situation obtains in regard to compounds (XXII) and (XXIII). With diazomethane these compounds gave the corresponding ethers, (XXII*a*) and (XXIII*a*) respectively, whereas with methyl sulphate and alkali they both gave (XXIII*a*) as the only product identified. The substance recovered from an alkaline solution of (XXII) or (XXIII) was oily and when induced to solidify was obviously heterogeneous but it gave impure (XXIII) on recrystallisation, and (XXIII*a*) on treatment with diazomethane. Thus in alkaline solution (XXIII) appears to predominate over (XXII).

The compound (XXIV), obtained in the course of hydroxylation of *o*-cresol (Part I, *loc. cit.*), has provided an interesting example of rearrangement. When it is dissolved in aqueous alkali acidification yields a mixture of (XXIV) and (XXV) in which the former

greatly predominates. Nearly complete rearrangement can be achieved, however, by adding a trace of alkali to a fairly concentrated solution of (XXIV) in ethanol whereupon the much less soluble (XXV) gradually crystallises. Although no convenient alternative synthesis of (XXV) is available, the structure assigned is supported by several observations. In concentrated sulphuric acid (XXV) affords a red solution indicative of the formation of a xanthylium salt, whereas with (XXIV) where analogous cyclisation is impossible the corresponding solution is pale yellow. Furthermore by methylation of (XXIV) and (XXV) with diazomethane and subsequent scission, in each case with piperidine, different methoxycresols were obtained and were recognised as 2-hydroxy-3-methoxy- and 3-hydroxy-2-methoxy-toluene respectively.

Scission of the 2-(2″-hydroxyaryloxy)-5-nitrobenzophenones and of their methyl ethers by piperidine was not attempted in all cases, but a number of catechol and guaiacol homologues, prepared in this way, are described in the Experimental section.

Experimental

2-Aryloxy-5-nitrobenzophenones (Table 1) were prepared by adding 2-chloro-5-nitrobenzophenone (1 mol.) to a fused mixture of the appropriate phenol (1·5—2 mol.) and potassium hydroxide (1·2 mol.). The mixture was warmed sufficiently to initiate and then to maintain the reaction (15—20 min.) before being cooled and treated with aqueous sodium hydroxide. The product was washed with water and crystallised first from acetic acid (diluted with water where necessary) and then from benzene (charcoal)–light petroleum (b. p. 50—80°).

2-(2″-Hydroxyaryloxy)-5-nitrobenzophonones (Table 2).—The finely powdered 2-aryloxy-5-nitrobenzophenone (0·0015 mole) was dissolved by shaking and gentle warming in 1 c.c. of concentrated sulphuric acid [0·5 c.c. for compounds (VIII), (IX), and (X)]. After ½ hour acetic acid (8 c.c.) was added and the mixture was treated with 30% hydrogen peroxide (*ca.* 0·002 mole) added dropwise and with shaking until, after 5 minutes, the original red colour lightened to a pale amber. The mixture was left for 20 minutes, then poured on crushed ice, and the washed and dried solid was crystallised from methanol. Compounds (XVI), (XVII), and (XXI) crystallised directly from the reaction mixtures and were further crystallised from ethanol. Compounds (XVIII) and (XIX) were crystallised from benzene–light petroleum (b. p. 60—80°), and the last traces of solvent could only be removed by melting the samples *in vacuo*.

Methylation of Compounds of Type (III).—(*a*) A solution of the compound in ether, containing a little methanol, was mixed with a large excess of diazomethane in ether and left at 0° for 2 days. Removal of the solvent gave the methylated product which was crystallised from ethanol. (*b*) The compound was treated with rather more than the minimum amount of 5% aqueous potassium hydroxide, and sufficient methanol was added where necessary to render the solution homogeneous at 0°. A slight excess of methyl sulphate was then added with shaking. The oil, initially formed, solidified on storage or when rubbed with ethanol from which the product was crystallised. The results are summaried in the following Table.

2-(2″-Methoxyaryloxy)-5-nitrobenzophenones.

					Found, %		Required, %	
No.	Subst.	M. p.	Source	Formula	C	H	C	H
XIV*a*	4″ : 6″-Me_2	131°	XIV * †	$C_{22}H_{19}O_5N$	70·1	5·2	70·0	5·1
XV*a*	3″ : 6″-Me_2	104	XV †	,,	70·1	5·5		
XVI*a*	4″ : 5″-Me_2	125	XVI †	,,	70·1	5·1		
XVII*a*	3″ : 5″-Me_2	101	XVII *	,,	70·0	5·0		
XXIII*a*	4″-Ph	120	XXIII *	$C_{26}H_{19}O_5N$	73·2	4·8	73·4	4·5
XXII*a*	5″-Ph	120	XXII * †	,,	73·7	4·5		
XXIV*a*	6″-Me	130	XXIV *	$C_{21}H_{17}O_5N$	69·6	4·8	69·4	4·7

In reaction with : * diazomethane, † methyl sulphate and alkali.

Rearrangements.—(XVII) ⟶ (XIV). Acidification of a solution of (XVII) in 5% aqueous potassium hydroxide, which had been kept at room temperature for 24 hours, afforded a gummy solid which, crystallised from methanol, had m. p. 106—108°, undepressed by admixture with (XIV) and depressed to m. p. 95—102° by admixture with (XVII). Methylation of (XVII) with methyl sulphate and alkali, but not with diazomethane (Table), involved rearrangement to the ether (XIV*a*), m. p. and mixed m. p. 131°, depressed to m. p. 85—90° by admixture with the methyl ether (XVII*a*).

(XXIII) —→ (XXII). Acidification of a solution of (XXIII) in 5% aqueous potassium hydroxide, which had been kept at room temperature for 1½ hours, afforded yellow crystals, m. p. 115° (from methanol), unchanged by admixture with the yellow form of (XXII) and depressed to m. p. 104—109° by admixture with (XXIII). Methylation of (XXIII) with methyl sulphate in alkali gave (XXII*a*), m. p. and mixed m. p. 120°, depressed to m. p. 103—110° by admixture with (XXIII*a*).

(XXIV —→ (XXV). (*a*) Acidification of a solution of (XXIV) in 5% aqueous potassium hydroxide, which had been kept at room temperature for 1 hour, yielded pale yellow crystals, m. p. 112—116° (once crystallised from methanol). After repeated crystallisations this material afforded 2-(2″-*hydroxy*-3″-*methylphenoxy*)-5-*nitrobenzophenone* (XXV) (*ca.* 10%) as colourless needles of m. p. 144—145°, depressed to m. p. 110—115° by admixture with (XXIV) (Found: C, 68·65; H, 4·25. $C_{20}H_{15}O_5N$ requires C, 68·8; H, 4·3%). (*b*) To an almost saturated solution of (XXIV) in methanol at room temperature was added a small drop of N-sodium hydroxide. Crystallisation, initiated by stirring or rubbing, proceeded slowly and gave (XXV) (90%), m. p. and mixed m. p. 144—145°.

Scissions with Piperidine.—The 2-(2″-hydroxy- or 2″-methoxy-aryloxy)-5-nitrobenzophenone was heated under reflux with piperidine for 1 hour and the product was recovered by method (*a*) for guaiacols and method (*b*) for catechols. (*a*) The cooled piperidine solution was diluted with benzene and was washed with dilute sulphuric acid and then with dilute sodium hydroxide solution. The acidified alkaline extract afforded the guaiacol on recovery in ether or chloroform. The crude product was distilled or sublimed *in vacuo* and, where practicable, crystallised from light petroleum or from benzene–light petroleum (b. p. 60—80°). (*b*) The cooled piperidine solution, diluted with benzene, was washed with water several times and the aqueous extract was acidified. The catechol was recovered from this solution in ether or chloroform and was purified as for the guaiacols. The following were thus prepared.

3: 5-Dimethylcatechol, m. p. 55° rising to 70·5—71° on prolonged storage over concentrated sulphuric acid; from (XVII) (Hodgkinson and Limpach, *J.*, 1903, **63**, 108, record m. p. 73—74° after dehydration).

3: 6-*Dimethylcatechol*, m. p. 104° (Found: C, 69·3; H, 7·7. $C_8H_{10}O_2$ requires C, 69·55; H, 7·3%); from (XV).

4: 5-Dimethylcatechol, m. p. 85—86° (Diepolder, *Ber.*, 1909, **42**, 2916, gives m. p. 79—82°; Karrer and Schick, *Helv. Chim. Acta*, 1943, **26**, 800, give m. p. 86—87°); from (XVI).

3-*Phenylcatechol*, m. p. 111° (Found: C, 77·2; H, 5·3. $C_{12}H_{10}O_2$ requires C, 77·4; H, 5·4%); from (XXI).

4-Phenylcatechol, m. p. 135° (Found: C, 77·55; H, 5·4%) (Yasuo, *Bull. Chem. Soc. Japan*, 1943, **18**, 93, records m. p. 141°); from (XXII) and (XXIII).

2-Methoxy-**3**: 5-dimethylphenol, a viscous liquid, b. p. 180° (bath-temp.)/20 mm. (Found: C, 70·7; H, 8·2. Calc. for $C_9H_{12}O_2$: C, 71·0; H, 7·95%) (Hodgkinson and Limpach, *loc. cit.*, record b. p. 227—228°); from (XVII*a*).

2-*Methoxy*-**3**: 6-*dimethylphenol*, m. p. 48° (Found: C, 70·8; H, 7·8%); from (XV*a*).

2-*Methoxy*-**4**: 6-*dimethylphenol*, m. p. 29° (Found: C, 70·75; H, 8·4%); from (XIV*a*).

2-*Methoxy*-5-*phenylphenol*, m. p. 111° (Found: C, 78·3; H, 6·0. $C_{13}H_{12}O_2$ requires C, 78·0; H, 6·0%); from (XXII*a*).

2-Hydroxy-3-methoxytoluene, m. p. 41° (Majima and Okazaki, *Ber.*, 1916, **49**, 1488, give m. p. 41—42°); from (XXIV*a*).

3-Hydroxy-2-methoxytoluene, m. p. 36·5°, was prepared by scission of the non-crystalline methyl ether of (XXV) obtained by treating the latter compound with diazomethane (Limpach, *Ber.*, 1891, **24**, 4137, gives m. p. 39° for the toluene). A mixed m. p. with the preceding isomer was *ca.* 25°.

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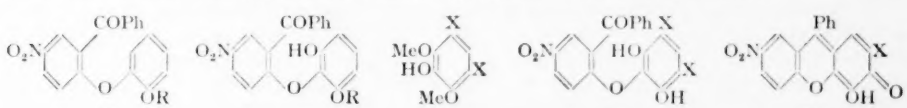
55. ortho-*Hydroxylation of Phenols. Part III.* Derivatives of Pyrogallol.*

By J. D. Loudon and J. A. Scott.

By the method developed earlier,* hydroxylation of 2-(2″-hydroxyaryloxy)-5-nitrobenzophenones, *e.g.*, (I; R = H), affords 2-(2″ : 6″-dihydroxyaryloxy)-5-nitrobenzophenones, *e.g.*, (II; R = H). When heated with piperidine the latter compounds undergo rearrangement with cyclisation to xanthen derivatives which are conveniently isolated as fluorones, *e.g.*, (V; X = H). This process is blocked by the presence of methyl (but not by bromo-)substituents in the 3″ : 5″-positions, allowing normal scission to 4 : 6-dimethylpyrogallol. It is also prevented by methylation (or toluenesulphonation) of the hydroxyl groups, the ethers being cleaved to partial methyl ethers of pyrogallol.

These observations have been combined in a synthesis of 1 : 2 : 3 : 4-tetramethoxybenzene, representing three consecutive hydroxylations of phenol.

The process used for hydroxylating phenols to the corresponding catechols * affords intermediates of type (I; R = H or Me). These should be capable of renewed hydroxylation to (II; R = H or Me) thereby providing a useful method of converting phenols ultimately into simple derivatives of pyrogallol. To test this expectation a solution of the guaiacol derivative (I; R = Me) in concentrated sulphuric acid was successively treated with acetic acid and hydrogen peroxide. The hydroxylation product (II; R = Me) was not obtained crystalline and similar reluctance to crystallise was later found to be general in partial methyl ethers of the class. Nevertheless, scission of the crude product with piperidine yielded pyrogallol 1-methyl ether which was characterised as the diacetate and dibenzoate, the erroneous description of the latter ester (Herzig and Klimosch, *Monatsh.*, 1909, **30**, 539) being incidentally corrected. Moreover, methylation of (II; R = Me) afforded the crystalline 2-(2″ : 6″-dimethoxyphenoxy)-5-nitrobenzophenone which, on scission with piperidine, yielded pyrogallol 1 : 3-dimethyl ether.



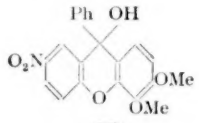
The catechol derivative (I; R = H) was smoothly hydroxylated to the pyrogallol derivative (II; R = H), the structure of which was confirmed by methylation to the 2″ : 6″-dimethoxy-compound. Scission of (II; R = H) with piperidine, however, could not be achieved since here dehydration intervened, leading ultimately to a highly coloured crystalline product which is considered to be the fluorone derivative (V; X = H). This interpretation is consistent with related observations outlined below. It assumes in (II; R = H) migration of the benzoylated nitrophenyl radical to an adjacent oxygen atom—a process known to occur in alkaline media (Part II)—and subsequent cyclisation involving the reactive *p*-position of a phenolic ion. Attempts to block the latter phase by bromination were unsuccessful. Bromination of (II; R = H) yielded a dibromo-derivative which is formulated as (IV; X = Br) since by methylation with diazomethane followed by scission with piperidine it afforded a dibromopyrogallol dimethyl ether (III; X = Br). On treatment with piperidine (IV; X = Br) yielded a monobromo-dehydration product (V; X = Br), one bromine atom having been eliminated during cyclisation.

The compounds just described form a series ultimately derived from phenol as parent substance and a similar series of products was obtained starting from *p*-cresol. Here also, following the second hydroxylation step, the product of attempted scission was of the

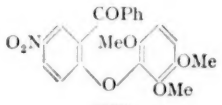
* Part II, preceding paper.

fluorone type and bromination of the appropriate intermediate was again ineffective in preventing cyclisation. In this series the orientation of the bromo-substituents in the methyl homologues of (III; X = Br), (IV; X = Br), and (V; X = Br) is unequivocally determined since the bromine atoms occupy the only free positions of the original tolyl nucleus. By successive hydroxylation and treatment with piperidine, homologues of (V; X = H) were likewise produced from 2-(2″-hydroxy-3″-methylphenoxy)- and 2-(2″-hydroxy-4″ : 5″-dimethylphenoxy)-5-nitrobenzophenone, compounds which are derived from *o*-cresol and 3 : 4-dimethylphenol respectively (Part II). A more interesting case is provided in 3 : 5-dimethylphenol as starting compound since in the intermediate (IV; X = Me), produced at the second hydroxylation stage, fluorone formation is blocked by the methyl substituents. In this case normal scission with piperidine occurred and 4 : 6-dimethylpyrogallol (as III; X = Me; HO for each MeO) was isolated.

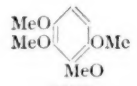
Closer examination of the process by which the fluorone (V; X = H) is produced from (IV; X = H) revealed that dehydration occurs only or mainly during removal of excess of piperidine by treatment with acid. When the amine was removed from the reaction mixture by water in presence of benzene a tar was precipitated, which yielded the fluorone when treated with acid and reacted with diazomethane in ether–methanol forming 3 : 4-dimethoxy-7-nitro-9-phenylxanthhydrol (VI). Incomplete removal of piperidine before methylation led to another product—apparently containing piperidine—but it also yielded the xanthhydrol (VI) on treatment with sulphuric acid. Oxidation of the xanthhydrol (VI) by hydrogen peroxide in sulphuric–acetic acid gave an uncrystallisable gum. This, however, on methylation afforded crystalline 2-(2″ : 3″ : 6″-trimethoxyphenoxy)-5-nitrobenzophenone (VII) which by scission with piperidine and renewed methylation yielded 1 : 2 : 3 : 4-tetramethoxybenzene (VIII), identical with a sample supplied by Professor W. Baker, F.R.S., whom we warmly thank.



(VI)



(VII)



(VIII)

These results accordingly show that, although compounds of type (I; R = H) may be hydroxylated to those of type (II; R = H), the latter in general are rearranged and cyclised by piperidine rather than cleaved to pyrogallols. On the other hand the mono- and the di-methyl ethers derived from type (II; R = H) undergo normal scission. Similarly cleavage of the ditoluene-*p*-sulphonate of (II; R = H) yielded a compound which was characterised by further acylation to pyrogallol tritoluene-*p*-sulphonate and is regarded as pyrogallol 1 : 3-ditoluene-*p*-sulphonate. Preliminary tests showed, however, that neither acetylation nor benzoylation of (II; R = H) effectively suppressed fluorone formation in subsequent reaction with piperidine.

Experimental

Pyrogallol Methyl Ethers.—To a cold solution of 2-(2″-methoxyphenoxy)-5-nitrobenzophenone (0·5 g.) in concentrated sulphuric acid (1 c.c.), acetic acid (8 c.c.) and then dropwise 30% hydrogen peroxide (0·5 c.c.) were added. When the original red colour had faded to amber, the mixture was poured on crushed ice, yielding an uncrystallisable flocculent yellow precipitate (II; R = Me). This was heated under reflux with piperidine (½ hour), cooled, diluted with benzene, and repeatedly extracted with water. From the aqueous extract after acidification, pyrogallol 1-methyl ether was recovered in chloroform: it distilled *in vacuo* as an oil which afforded the diacetate, m. p. 91—92° (Herzig and Pollak, *Monatsh.*, 1904, **25**, 508, give m. p. 91—93°), and the *dibenzoate*, m. p. 83° (from ethanol) (Found: C, 72·5; H, 4·6. $C_{21}H_{16}O_5$ requires C, 72·4; H, 4·6%). The dibenzoate, prepared from authentic pyrogallol 1-methyl ether (Hilleman, *Ber.*, 1938, **71**, 34) and benzoyl chloride in pyridine, had m. p. and mixed m. p. 83° whereas Herzig and Klimosch (*loc. cit.*) erroneously record m. p. 156—158° for the compound prepared in an ambiguous way.

With methyl sulphate in alkali, (II; R = Me) afforded 2-(2″ : 6″-*dimethoxyphenoxy*)-5-

nitrobenzophenone as cubes, m. p. 170°, from ethanol (Found: C, 66·5; H, 4·7. $C_{21}H_{17}O_6N$ requires C, 66·5; H, 4·5%). This compound was cleaved by hot piperidine and, from the acid-washed benzene solution of the products, pyrogallol 1 : 3-dimethyl ether was extracted by alkali, recovered in ether, distilled, and identified as the benzoate, m. p. 115° (Hofmann, *Ber.*, 1879, **12**, 1373, records m. p. 118°).

2-(2″ : 6″-*Dihydroxyphenoxy*)-5-*nitrobenzophenone* (II; R = H).—The red solution obtained by warming 2-(2″-hydroxyphenoxy)-5-nitrobenzophenone (0·5 g.) in concentrated sulphuric acid (0·5 c.c.) was cooled and acetic acid (8 c.c.) and then, dropwise with shaking, 30% hydrogen peroxide (0·5 c.c.) were added. When the colour became amber (10 min.) the mixture was poured on ice and afforded 2-(2″ : 6″-*dihydroxyphenoxy*)-5-*nitrobenzophenone* as yellow crystals, m. p. 180° (decomp.), from methanol (Found: C, 65·1; H, 3·85. $C_{19}H_{13}O_6N$ requires C, 65·0; H, 3·7%). It reacted (*a*) with ethereal diazomethane forming the dimethyl ether, m. p. and mixed m. p. 170°; (*b*) with toluene-*p*-sulphonyl chloride in pyridine (15 min. at 100°), forming the *ditoluene*-p-*sulphonate*, colourless prisms of m. p. 144° (from ethanol) (Found: C, 60·0; H, 4·0. $C_{33}H_{25}O_{10}NS_2$ requires C, 60·1; H, 3·8%), and (*c*) with bromine in chloroform, affording the 3″ : 5″-*dibromo*-derivative (IV; X = X = Br), pale yellow needles of m. p. 206° (from benzene) (Found: C, 44·9; H, 2·3. $C_{19}H_{11}O_6NBr_2$ requires C, 44·8; H, 2·2%).

4-*Hydroxy*-7-*nitro*-9-*phenylfluorone* (V; X = H).—The maroon-coloured precipitate, obtained by boiling (II; R = H) with piperidine (2 min.) and pouring the cooled solution into dilute sulphuric acid, was dried and warmed with anisole. After being decanted from tar the anisole solution deposited the *fluorone* as stout black needles, m. p. 320° (decomp.) (Found: C, 68·2; H, 3·4. $C_{19}H_{11}O_5N$ requires C, 68·5; H, 3·3%).

3-*Bromo*-4-*hydroxy*-7-*nitro*-9-*phenylfluorone* (V; X = Br), black needles, m. p. 324° (decomp.) (from anisole), was similarly prepared from (IV; X = Br) (Found: C, 55·5; H, 2·7. $C_{19}H_{10}O_5NBr$ requires C, 55·4; H, 2·45%).

Toluene-p-*sulphonates of Pyrogallol.*—The ditoluene-*p*-sulphonate of (II; R = H) was heated (1 hour) with piperidine, and an acid-washed benzene solution of the products was shaken with dilute sodium hydroxide. The sodium salt thereby precipitated was treated with acid in presence of chloroform from which *pyrogallol* 1 : 3-*ditoluene*-p-*sulphonate* was recovered as prisms, m. p. 126° (methanol) (Found: C, 55·1; H, 4·1. $C_{20}H_{18}O_7S_2$ requires C, 55·3; H, 4·2%). With toluene-*p*-sulphonyl chloride in pyridine (15 min. at 100°) this formed the *tritoluene*-p-*sulphonate*, prisms, m. p. 139° (from ethanol), identical with a sample prepared directly from pyrogallol (Found: C, 54·9; H, 4·05. $C_{27}H_{24}O_9S_3$ requires C, 55·1; H, 4·1%).

4 : 6-*Dibromopyrogallol* 1 : 3-*Dimethyl Ether.*—2-(3″ : 5″-*Dibromo*-2″ : 6″-*dimethoxyphenoxy*)-5-*nitrobenzophenone*, colourless needles, m. p. 139° (from ethanol) (Found: C, 47·05; H, 2·7. $C_{21}H_{15}O_6NBr_2$ requires C, 46·95; H, 2·8%), was formed from (IV; X = Br) and ethereal diazomethane. Treated with piperidine as described for the unbrominated compound, it yielded 4 : 6-*dibromopyrogallol* 1 : 3-*dimethyl ether* as needles, m. p. 132°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 31·0; H, 2·7. $C_8H_8O_3Br_2$ requires C, 30·8; H, 2·6%).

2-(2″ : 6″-*Dihydroxy*-4″-*methylphenoxy*)-5-*nitrobenzophenone*, obtained by hydroxylating 2-(2″-hydroxy-4″-methylphenoxy)-5-nitrobenzophenone, formed yellow prisms, m. p. 166° (decomp.), from chloroform (Found: C, 65·9; H, 4·3. $C_{20}H_{15}O_6N$ requires C, 65·5; H, 4·1%). It afforded (*a*) with methyl sulphate in alkali 2-(2″ : 6″-*dimethoxy*-4″-*methylphenoxy*)-5-*nitrobenzophenone*, colourless prisms, m. p. 200—201° (from ethanol) (Found: C, 66·9; H, 4·7. $C_{22}H_{19}O_6N$ requires C, 67·15; H, 4·9%), likewise produced from the pink uncrystallisable solid obtained by hydroxylating 2-(2″-methoxy-4″-methylphenoxy)-5-nitrobenzophenone; (*b*) with bromine in chloroform, the 3″ : 5″-*dibromo*-derivative, yellow cubes, m. p. 204° (from ethanol) (Found: C, 46·0; H, 2·5. $C_{20}H_{13}O_6NBr_2$ requires C, 45·9; H, 2·5%); and (*c*) with hot piperidine and subsequent treatment with acid, 4-*hydroxy*-1-*methyl*-7-*nitro*-9-*phenylfluorone*, m. p. 277° (decomp.) (from anisole) (Found: C, 69·0; H, 3·6. $C_{20}H_{13}O_5N$ requires C, 69·2; H, 3·8%). When the 3″ : 5″-dibromo-compound (cf. *b*) was used in reaction (*c*), 3-*bromo*-4-*hydroxy*-1-*methyl*-7-*nitro*-9-*phenylfluorone* was produced and had m. p. 300° (decomp.) (Found: C, 56·5; H, 3·0. $C_{20}H_{12}O_5NBr$ requires C, 56·4; H, 2·8%).

4 : 6-*Dibromo*-5-*methylpyrogallol* 1 : 3-*dimethyl ether* was obtained as colourless needles, m. p. 130° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 33·1; H, 3·0. $C_9H_{10}O_3Br_2$ requires C, 33·2; H, 3·1%), by the action of piperidine on 2-(3″ : 5″-*dibromo*-2″ : 6″-*dimethoxy*-4″-*methylphenoxy*)-5-*nitrobenzophenone*, m. p. 144° (from ethanol) (Found: C, 48·2; H, 2·9. $C_{22}H_{17}O_6NBr$ requires C, 47·9; H, 3·1%), which in turn was prepared by direct bromination or by (diazomethane) methylation of the brominated 2″ : 6″-dihydroxy-compound.

4-*Hydroxy*-2-*methyl*-7-*nitro*-9-*phenylfluorone*, m. p. 295° (decomp.) (from anisole) (Found: C, 69·5; H, 3·9. $C_{20}H_{13}O_5N$ requires C, 69·2; H, 3·8%), was formed when the crude hydroxylation product (m. p. 106°) from 2-(2″-hydroxy-3″-methylphenoxy)-5-nitrobenzophenone was heated with piperidine and the cooled solution was poured into dilute sulphuric acid.

4-*Hydroxy*-1 : 2-*dimethyl*-7-*nitro*-9-*phenylxanthhydrol*, yellowish prisms, m. p. 221° (from aqueous acetic acid) (Found: C, 69·1; H, 4·9. $C_{21}H_{17}O_5N$ requires C, 69·4; H, 4·7%), was formed when the red solution of 2-(2″-hydroxy-4″ : 5″-dimethylphenoxy)-5-nitrobenzophenone in concentrated sulphuric acid was poured on ice.

2-(2″ : 6″-*Dihydroxy*-3″ : 4″-*dimethylphenoxy*)-5-*nitrobenzophenone* was obtained from the sulphuric acid solution of the foregoing experiment by the addition of acetic acid, an intense blue colour being developed; this faded to amber on subsequent addition of hydrogen peroxide, whereupon the whole was poured on ice. It formed yellow prisms, m. p. 175° (decomp.), from benzene–light petroleum (b. p. 60—80°) (Found: C, 66·6; H, 4·5. $C_{21}H_{17}O_6N$ requires C, 66·5; H, 4·5%), and, by heating with piperidine followed by treatment with cold dilute sulphuric acid, afforded 4-*hydroxy*-1 : 2-*dimethyl*-7-*nitro*-9-*phenylfluorone* as glistening black needles, m. p. 300° (decomp.), from anisole (Found: C, 69·7; H, 4·4. $C_{21}H_{15}O_5N$ requires C, 69·8; H, 4·2%).

2-(2″-*Hydroxy*-6″-*methoxy*-3″ : 4″-*dimethylphenoxy*-5-*nitrobenzophenone*, which crystallised, with difficulty, as orange-yellow prisms, m. p. 149°, from methanol (Found: C, 67·35; H, 5·0. $C_{22}H_{19}O_6N$ requires C, 67·15; H, 4·9%), was prepared by adding hydrogen peroxide to the blue-green solution of 2-(2″-methoxy-4″ : 5″-dimethylphenoxy)-5-nitrobenzophenone (0·5 g.) in sulphuric–acetic acid (0·5 : 8 c.c.) and, after 5 min., pouring the filtered solution on ice.

2-(2″ : 6″-*Dihydroxy*-3″ : 5″-*dimethylphenoxy*)-5-*nitrobenzophenone* (IV; X = X = Me), colourless needles, m. p. 196° (from ethanol) (Found: C, 66·5; H, 4·5. $C_{21}H_{17}O_6N$ requires C, 66·5; H, 4·5%), was prepared by adding hydrogen peroxide to the purple solution of 2-(2″-hydroxy-3″ : 5″-dimethylphenoxy)-5-nitrobenzophenone in sulphuric–acetic acid and pouring the resultant mixture on ice.

4 : 6-*Dimethylpyrogallol*, prepared from the foregoing compound as described for pyrogallol 1-methyl ether, was sublimed at 80°/3 mm. and formed colourless needles, m. p. 123°, from benzene (Found: C, 62·5; H, 6·7. $C_8H_{10}O_3$ requires C, 62·4; H, 6·5%).

3 : 4-*Dimethoxy*-7-*nitro*-9-*phenylxanthhydrol* (VI).—The solution obtained by heating (IV; X = H) with piperidine for 2 min., cooling, and diluting with benzene, was washed with water (*a*) exhaustively, whereupon a tar separated, or (*b*) until the tar just began to form. In the former case the tar, separated by decantation and dried *in vacuo*, was treated with ethereal diazomethane and after some hours the *xanthhydrol* (VI) was recovered from the resultant yellow solution. It formed colourless needles, m. p. 184°, from benzene (charcoal)–light petroleum (b. p. 60—80°) (Found: C, 66·3; H, 4·7. $C_{21}H_{17}O_6N$ requires C, 66·5; H, 4·5%), and in acetic acid, saturated with hydrogen chloride, gave with ferric chloride red plates of the chloride-ferrichloride, or afforded with perchloric acid in acetic acid red needles of the perchlorate.

In case (*b*), evaporation of the dried benzene solution and subsequent methylation gave yellow prisms, m. p. 227°, which have not yet been identified (Found: C, 67·3; H, 6·45; N, 6·3. $C_{21}H_{17}O_6N,C_5H_{11}N$ requires C, 67·3; H, 6·1; N, 6·0). The *substance* yielded the xanthhydrol (VI) when its solution in concentrated sulphuric acid was poured on ice but could not be prepared by heating (VI) with piperidine or from the fluorone (V; X = H) by similar treatment followed by methylation.

1 : 2 : 3 : 4-*Tetramethoxybenzene*.—The flocculent precipitate, produced by adding hydrogen peroxide (0·2 c.c.) to a solution of (VI) (0·2 g.) in concentrated sulphuric–acetic acid (0·25 : 3·5 c.c.) and pouring the whole on ice, could not be crystallised but with methyl sulphate in alkali gave 2-(2″ : 3″ : 6″-*trimethoxyphenoxy*)-5-*nitrobenzophenone* as pale yellow prisms, m. p. 134° (from methanol) (Found: C, 64·4; H, 4·9. $C_{22}H_{19}O_7N$ requires C, 64·5; H, 4·7%). This compound was heated (1 hour) with piperidine, benzene was added, and the solution was successively extracted with dilute sulphuric acid and alkali. To the alkaline extract methyl sulphate was added with shaking and, after brief heating, tetramethoxybenzene was recovered in chloroform as colourless prisms, (micro-)m. p. 85° and mixed m. p. 85—86° with an authentic sample (Found: C, 60·5; H, 6·95. Calc. for $C_{10}H_{14}O_4$: C, 60·0; H, 7·1%). Baker, Jukes, and Subrahmanyam (*J.*, 1934, 1683) record m. p. 89°.

7-*Nitro*-9-*phenylfluorone*.—When 2-(3″-*methoxyphenoxy*)-5-*nitrobenzophenone*, prisms, m. p. 100° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 68·7; H, 4·6. $C_{20}H_{13}O_5N$ requires C, 68·8; H, 4·3%), was heated for 2½ hours with constant-boiling hydrobromic acid

in acetic acid, and the cooled solution was poured into water, *7-nitro-9-phenylfluorone* was obtained as orange needles, m. p. 308° (from benzene) (Found: C, 71·9; H, 3·9. $C_{19}H_{11}O_4N$ requires C, 71·9; H, 3·5%).

The authors gratefully acknowledge their indebtedness to Imperial Chemical Industries Limited, Explosives Division, Ardeer, for gifts of phenols, and to the Department of Scientific and Industrial Research for a Maintenance Allowance (to J. A. S.). Microanalyses were carried out by Mr. J. M. L. Cameron, Miss R. H. Kennaway, and Miss M. W. Christie.

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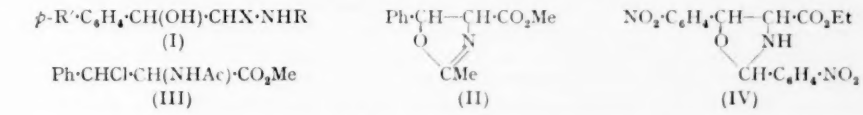
56. *Some Derivatives of β-Phenylserine.*

By D. O. HOLLAND, P. A. JENKINS, and J. H. C. NAYLER.

The possible inversion of the diastereoisomeric β-phenyl- and β-*p*-nitrophenyl-serines has been briefly studied and several *p*-substituted phenylserines have been prepared.

DURING our study of derivatives of β-phenylserine (I; R = R′ = H, X = CO_2H), considered as analogues of the antibiotic chloramphenicol (I; *threo*; R = $CO{\cdot}CHCl_2$, R′ = NO_2, X = $CH_2{\cdot}OH$), reports of similar investigations appeared from several sources. This paper therefore records only that part of our work which has not been adequately described elsewhere: our conclusions regarding the two *p*-nitrophenylserines have been previously but briefly published (Holland and Jenkins, *Chem. and Ind.*, 1951, 1092; Holland and Nayler, *ibid.*, 1952, 518).

Although *threo*-phenylserine, the configuration of which has been determined by Billet (*Compt. rend.*, 1950, **230**, 1074) and by Vogler (*Helv. Chim. Acta*, 1950, **33**, 2111), has been known for some time the pure *erythro*-form had not been described when our work began and attempts were made to prepare it by inversion of the *threo*-isomer. Satisfactory methods for the preparation of *erythro*-phenylserine have since been reported by Shaw and Fox (Abstr., 118th A.C.S. meeting, 1950, p. 28N) and by Elphimoff-Felkin *et al.*, (*Compt. rend.*, 1951, **232**, 241; *Bull. Soc. chim.*, 1952, **19**, 252).



Attempts to effect inversion at the β-carbon atom of *N*-acetyl-*threo*-phenylserine methyl ester *via* the *cis*-oxazoline (II) by reaction with thionyl chloride gave the β-chloro-derivative (III) as the only tractable product, even at −20° when some starting material remained unchanged. Treatment of the reaction product with pyridine, as described by Fry (*J. Org. Chem.*, 1950, **15**, 438) for the preparation of methyl 2-phenyl-L-oxazoline-4-carboxylate, also failed since the only transformation products isolated were the chloro-compound (III) and methyl α-acetamidocinnamate [no doubt formed from (III) by removal of hydrogen chloride]. Vogler (*loc. cit.*) similarly obtained a β-chloro-compound rather than an oxazoline from the corresponding ethyl ester, although Moersch, Rebstock, Moore, and Hylander (*J. Amer. Chem. Soc.*, 1952, **74**, 565) inverted *erythro-p*-nitrophenylserine by the oxazoline route.

The action of moist silver carbonate on (III) gave the original *N*-acetyl-*threo*-phenylserine methyl ester and since this reagent does not in general effect a Walden inversion it appears that the chloro-compound (III) also possesses the *threo*-configuration. Attempts to replace the chlorine of (III) by hydroxyl with inversion by the use of stronger bases were unsuccessful. Sodium hydroxide at ordinary temperature yielded mainly α-acetamidocinnamic acid together with an unsaturated neutral substance, $C_{10}H_{11}ON$, which

may have been acetamidostyrene or 2-methyl-5-phenyl-Δ^1-oxazoline. Sodium carbonate similarly removed hydrogen chloride to yield methyl α-acetamidocinnamate. This ester on hydrolysis with aqueous sodium hydroxide gave only the corresponding acid. The chlorine atom was also replaced by hydroxyl without inversion when (III) was converted by boiling dilute mineral acid into *threo*-phenylserine.

Two DL-forms of *p*-nitrophenylserine (I; R = H, R′ = NO_2, X = CO_2H) are known although their configurations have recently aroused controversy. Compounds of one series have been obtained by numerous workers by the nitration of *threo*-phenylserine or derivatives thereof; those of the other arise by a sequence of reactions from *p*-nitrobenzaldehyde and glycine ester. The latter reactants condense in ether in the presence of sodium (Dalgliesh, *J.*, **1949**, 90) or in alcohol without a catalyst (Bergmann, Genas, and Bendas, *Compt. rend.*, **1950**, **231**, 361; Bergmann, Bendas, and Taub, *J.*, **1951**, 2673) to yield a compound $C_{18}H_{17}O_7N_3$ tentatively regarded by Dalgliesh as the oxazolidine (IV) but which from its infra-red spectrum appears to be the isomeric Schiff's base (V) (Bergmann, Zimkin, and Pinchas, *Rec. Trav. chim.*, **1952**, **71**, 168). A compound, m. p. 148°, obtained earlier by Gerngross and Zühlke (*Ber.*, **1924**, **57**, 1482) from *p*-nitrobenzaldehyde and glycine ester in alcohol and considered by them to be *p*-nitrobenzylideneglycine ester appears also to be this *p*-nitrophenylserine derivative, since authentic *p*-nitrobenzylideneglycine ester has m. p. 85—88° (see below). We have found that the compound (V) is more conveniently prepared in alcohol in the presence of triethylamine. Conversion into *p*-nitrophenylserine was then effected in good overall yield essentially as described by Dalgliesh (*loc. cit.*).

That the *p*-nitrophenylserine obtained in this way differs from that derived by the nitration of *threo*-phenylserine is clear from their different biological activity (Billet, *loc. cit.*; Molho and Molho-Lacroix, *Compt. rend.*, **1951**, **233**, 1067) and from the distinctive melting points of several derivatives (Kopp, Larramona, and Welvart, *Compt. rend.*, **1951**, **233**, 527; Moersch *et al.*, *loc. cit.*). In addition we have found that the two isomers are readily separable by paper partition chromatography. Both forms of *N*-acetyl-*p*-nitrophenylserine, with acetic anhydride, yielded 2-methyl-4-*p*-nitrobenzylidene-5-oxazolone, which is also obtained when *p*-nitrobenzaldehyde and aceturic acid are heated with acetic anhydride and sodium acetate.

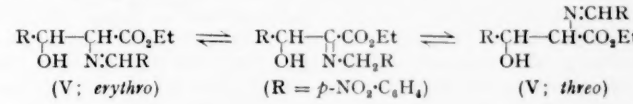
It has been generally assumed that the *p*-nitrophenylserine derived from *threo*-phenylserine itself has the *threo*-configuration and that the compounds derived from *p*-nitrobenzaldehyde are hence members of the *erythro*-series. In support of this, Kopp *et al.* (*loc. cit.*) described the preparation of an *ON*-diacetyl-*p*-nitrophenylserine ester from *erythro*-phenylserine, identical with the acetylation product of the *p*-nitrophenylserine ester obtained from *p*-nitrobenzaldehyde. It has, however, been claimed by Bergmann, Bendas, and Taub (*loc. cit.*) that condensation of *p*-nitrobenzaldehyde with glycine ester in alcohol gives compounds possessing the *threo*-configuration since lithium aluminium hydride reduction, presumably of the *p*-nitrophenylserine ester, apparently gave rise to *threo*-2-amino-1-*p*-nitrophenylpropane-1 : 3-diol (I; R = H, R′ = NO_2, X = CH_2·OH). Accordingly, we examined the lithium aluminium hydride reduction of compounds of both series and obtained *threo*-2-acetamido-1-*p*-nitrophenylpropane-1 : 3-diol (I; R = Ac, R′ = NO_2, X = CH_2·OH) from the ester of the nitration product of *N*-acetyl-*threo*-phenylserine and the *erythro*-diol from the acetyl derivative of the ester obtained from *p*-nitrobenzaldehyde. These results prove that the main product isolated from the condensation of *p*-nitrobenzaldehyde and glycine ester has the *erythro*-configuration. Attempts to reduce the unacetylated *erythro*-ester with lithium aluminium hydride were unsuccessful.

The claim by Billet and Marnay (*Compt. rend.*, **1951**, **233**, 961) to have obtained the *threo*-form, m. p. 89°, of the Schiff's base (V) by the uncatalysed reaction of *p*-nitrobenzaldehyde and glycine ester in dry ether is apparently unfounded since it has been shown independently by Elphimoff-Felkin, Felkin, and Welvart (*Compt. rend.*, **1952**, **234**, 1564) and by two of us (Holland and Nayler, *loc. cit.*) that the product is in fact *N*-*p*-nitrobenzylideneglycine ester. Authentic *N*-*p*-nitrobenzylidene-*threo*-*p*-nitrophenylserine ethyl ester prepared from *threo*-*p*-nitrophenylserine ester and *p*-nitrobenzaldehyde has m. p. 121—121·5°, evidence that this compound is not the isomeric oxazolidine (IV) being

afforded by the very close similarity of its ultra-violet absorption spectrum to that of the *erythro*-Schiff's base.

It is noteworthy that none of the various groups of workers who have condensed *p*-nitrobenzaldehyde with glycine ester has referred to the possibility of more than one form of *p*-nitrophenylserine derivative being present in a given reaction mixture. We have found, using paper chromatography, that the condensation in ethanol either with or without triethylamine gives rise to both *erythro*- and *threo*-compounds although the former are produced in greater quantity and, being the less soluble, constitute the form normally isolated. The erroneous conclusion by Bergmann, Bendas, and Taub (*loc. cit.*) as to the configuration of the major constituent may thus have been due to the reduction of a mixture of diastereoisomers and the fortuitous isolation of only the *threo*-form of the product.

The possibility that the two forms of *p*-nitrophenylserine might undergo inversion by way of the *N*-*p*-nitrobenzylidene derivatives of their esters was first suggested by Billet and Marnay (*loc. cit.*) to explain the spontaneous conversion in alcohol of a labile compound, m. p. 85°, obtained by Dalgliesh into the *erythro*-form of (V). Billet and Marnay considered the labile compound to be the *threo*-form of (V), but this has now been shown to have m. p. 121—121·5°. However, since inversion at the α-carbon atom of (V) could theoretically occur by prototropy as indicated below (cf. Harvill and Herbst, *J. Org. Chem.*, 1944, **9**, 21, and earlier papers) we briefly examined the behaviour of pure specimens of each diastereoisomer in ethanol.



After 1 hour's refluxing either pure Schiff's base was found to give rise on hydrolysis to a mixture of both forms of *p*-nitrophenylserine, but from the relative intensities of the spots on a paper chromatogram developed with ninhydrin the extent of inversion appeared to be fairly small. The prototropic mechanism advanced above suggested that a base might accelerate the attainment of equilibrium and it was found that in presence of 0·1 mol. of triethylamine each Schiff's base gave substantial amounts of each form of *p*-nitrophenylserine. There was, however, no clear evidence of preferential formation of one isomer. Similar results were obtained when the Schiff's bases were formed *in situ* by heating the *p*-nitrophenylserine esters with *p*-nitrobenzaldehyde and triethylamine in alcohol. It was established that the method of conversion into the amino-acids caused no appreciable inversion, although a little breakdown to glycine occurred during alkaline hydrolysis of the esters. Similarly the esters did not suffer significant inversion on brief heating with ethanolic triethylamine in the absence of aldehydes.

Elphimoff-Felkin, Felkin, and Welvart (*Compt. rend.*, 1952, **234**, 1627) recently recorded the conversion of the *threo*-ester into the *erythro*-Schiff's base and *vice versa*, and postulated a mechanism involving fission of the central carbon–carbon bond.

Several other substituted phenylserines have been prepared from the two *p*-nitrophenylserines. Catalytic hydrogenation afforded the two *p*-amino-compounds of which the *erythro*-isomer has been described by Dalgliesh, and these led by diazotisation to the hydroxy- and the chloro-compounds.

p-Hydroxyphenylserine was also prepared, in 15% overall yield, from *p*-(ethyl carbonato)benzaldehyde and glycine ester in the presence of sodium as described by Rosenmund and Dornsaft (*Ber.*, 1919, **52**, 1734). The configuration of the product could not be inferred from its melting point since those of the two *p*-hydroxyphenylserines differ by only a few degrees and, in common with the other diastereoisomeric pairs of amino-acids encountered in the present work, give no depression on admixture. Paper partition chromatography indicated, however, that it was probably *erythro*-*p*-hydroxyphenylserine.

In addition to the diazotisation method *threo*-*p*-chlorophenylserine was also obtained by direct condensation of *p*-chlorobenzaldehyde with glycine in aqueous-alcoholic sodium hydroxide.

None of these compounds possessed appreciable antibacterial activity.

Experimental

M. p.s are uncorrected.

N-Acetyl-threo-β-*phenylserine*.—To a solution of *threo*-phenylserine (36 g.) in N-sodium hydroxide (200 ml.), 2N-sodium hydroxide (520 ml.) and acetic anhydride (52 ml.) were run in concurrently with stirring during 1·5 hours while the temperature was kept at 0—5° and the mixture was kept alkaline. After storage at 0° overnight the filtered solution was acidified (pH 1) with concentrated hydrochloric acid and concentrated under reduced pressure to about 200 ml. On refrigeration the product separated almost quantitatively as colourless needles, m. p. 146—147° (decomp.), unchanged by recrystallisation from hot water (Weitnauer, *Gazzetta*, 1951, **81**, 156 gives m. p. 152°) (Found : C, 59·0; H, 5·9; N, 6·5. Calc. for $C_{11}H_{13}O_4N$: C, 59·2; H, 5·8; N, 6·3%).

Methyl ester. *N*-Acetyl-*threo*-phenylserine (20 g.) suspended in dry dioxan was treated with an excess of ethereal diazomethane with shaking and initial cooling. Next morning the excess of diazomethane was destroyed with acetic acid and the crude solid (19·3 g.) was collected and washed with ether. Recrystallisation from water (300 ml.)–alcohol (70 ml.) yielded the *ester* (15·4 g.), constant m. p. 174—180° (decomp.) (Found : C, 60·3; H, 6·6; N, 6·1. $C_{12}H_{15}O_4N$ requires C, 60·8; H, 6·3; N, 5·9%).

Methyl α-Acetamido-β-chloro-β-phenylpropionate.—Thionyl chloride (40 ml.) was added dropwise during 1 hour to a stirred suspension of *N*-acetyl-*threo*-phenylserine methyl ester (20 g.) in dry chloroform (20 ml.) at about 0°. After being kept overnight at 0° the solution was concentrated under reduced pressure at room temperature and the remaining red syrup was diluted with chloroform and extracted with 5 small portions of water. Evaporation of the dried chloroform layer yielded a dark brown syrup, which solidified when rubbed with ethyl acetate. The yellow solid was washed with ethyl acetate–ether (1 : 1) and finally ether, to yield 9·05 g. of *methyl α-acetamido-β-chloro-β-phenylpropionate*. A further 0·82 g. was obtained by concentration of the filtrates and cautious dilution with ether. Recrystallisation from 50% aqueous alcohol gave a white powder, m. p. 128—128·5° (Found : C, 56·6; H, 5·7; N, 5·1; Cl, 13·7. $C_{12}H_{14}O_3NCl$ requires C, 56·4; H, 5·5; N, 5·5; Cl, 13·9%).

Action of Bases on Methyl α-Acetamido-β-chloro-β-phenylpropionate (III).—(a) *Silver carbonate*. To a solution of silver nitrate (0·74 g.) in water (2·5 ml.) there was added aqueous potassium carbonate (0·3 g. in 2·5 ml.), followed by alcohol (5 ml.) and the β-chloro-ester (1 g.). The mixture was heated under reflux for 4 hours, filtered, and concentrated under reduced pressure; *N*-acetyl-*threo*-phenylserine methyl ester (0·25 g.) separated, having m. p. 174—180° not depressed by an authentic specimen.

(b) *Sodium hydroxide*. A mixture of the chloro-ester (2·55 g.) with 1·01N-sodium hydroxide (24·7 ml.) and dioxan (10 ml.) was shaken for 1 hour, and the resulting clear solution kept at ordinary temperature for 2 days, then concentrated under reduced pressure to a small volume; some white solid separated. This was removed, washed with water, and dried *in vacuo* ($CaCl_2$), to yield 0·44 g., m. p. 113—114° with slight gas evolution. After several crystallisations from carbon tetrachloride and from aqueous alcohol, followed by sublimation *in vacuo*, the *substance* had m. p. 113—117°, after shrinking from 106° (Found : C, 74·4; H, 6·5; N, 9·1. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·8; N, 8·7%). It rapidly decolorised bromine water.

The alkaline filtrate on acidification evolved carbon dioxide and deposited α-acetamidocinnamic acid (1·32 g., 64%), m. p. 186—188° (decomp.) after crystallisation from water and drying at 80°/0·5 mm. (P_2O_5) (Found : C, 64·1; H, 5·6; N, 7·1. Calc. for $C_{11}H_{11}O_3N$: C, 64·4; H, 5·4; N, 6·8%). Erlenmeyer and Früstück (*Annalen*, 1895, **284**, 47) gave m. p. 190—191° (decomp.) for the anhydrous acid. This, when heated with acetic anhydride, yielded its azlactone, m. p. 153—154°, identical with the compound obtained on heating phenylserine with the same reagent (Bergmann and Delis, *ibid.*, 1927, **458**, 76).

(c) *Sodium carbonate*. The chloro-ester (1·5 g.) and sodium carbonate (0·34 g.) in 50% aqueous dioxan (40 ml.) were refluxed for 3 hours and concentrated *in vacuo* to a small volume. A gum separated which solidified. This crude *methyl α-acetamidocinnamate* (1·05 g.) was crystallised several times from benzene and then had m. p. 124—127° (slight decomp.) (Found : C, 65·3; H, 6·1. $C_{12}H_{13}O_3N$ requires C, 65·8; H, 5·9%). It rapidly decolorised bromine water, and when shaken with N-sodium hydroxide yielded α-acetamidocinnamic acid almost quantitatively.

Action of Dilute Hydrochloric Acid on (III).—The chloro-ester (2 g.) was refluxed in 10% hydrochloric acid (30 ml.) for 4 hours, developing an odour of phenylacetaldehyde, and after extraction with ethyl acetate was evaporated *in vacuo*, treated with water and concentrated

again. The residual gum was dissolved in a little water, an excess of triethylamine added, the mixture evaporated *in vacuo*, and the residue washed with chloroform to remove triethylamine hydrochloride and leave crude *threo*-phenylserine (1·07 g.), characterised as the *N*-acetyl derivative.

threo-β-p-*Nitrophenylserine*.—*N*-Acetyl-*threo*-phenylserine was nitrated essentially as described by Woolley (*J. Biol. Chem.*, 1950, **185**, 293) except that 0·3 mol. of sodium nitrite was included in the cold fuming nitric acid. The resulting *N*-acetyl-*threo*-*p*-nitrophenylserine (67·5%) separated from aqueous alcohol as cream-coloured crystals, m. p. 191—192° (decomp.) (Found: C, 49·1; H, 4·9; N, 10·0. Calc. for $C_{11}H_{12}O_6N_2$: C, 49·3; H, 4·5; N, 10·4%). Hydrolysis was accomplished in 72% yield essentially as described by Woolley, the amino-acid crystallising from water (charcoal) as a cream-coloured powder, m. p. 180—181° (decomp.) (dependent considerably on the rate of heating). Analysis indicated 1·5 mol. of water of crystallisation (Billet, *loc. cit.*, reported only 1 mol.) (Found: C, 42·8; H, 5·15; N, 10·7. Calc. for $C_9H_{10}O_5N_2,1{\cdot}5H_2O$: C, 42·7; H, 5·14; N, 11·1%).

erythro-β-p-*Nitrophenylserine*.—A solution of glycine ethyl ester hydrochloride (43·5 g.) in hot absolute alcohol (250 ml.) was added to a solution of sodium (7·15 g.) in absolute alcohol (175 ml.) and after 1 hour sodium chloride was removed. To the filtrate was added *p*-nitrobenzaldehyde (93·9 g.) followed by triethylamine (4·5 ml.), and the mixture shaken occasionally until the reaction appeared to be virtually complete. Next morning the intermediate *p*-nitrobenzylidene derivative (V), m. p. 142—143°, was filtered off, washed with alcohol and then ether (yield 99·6 g., 82%). A sample recrystallised from methanol or benzene formed colourless needles, m. p. 146—147° (Found: C, 55·8; H, 4·3; N, 11·0. Calc. for $C_{18}H_{17}O_7N_3$: C, 55·8; H, 4·4; N, 10·8%).

The intermediate (133·2 g.) was heated under reflux with absolute alcohol (1330 ml.), and 2·58N-alcoholic hydrochloric acid (201 ml., 1·5 equiv.) was added to the boiling suspension. Dissolution was rapid and after about 2 minutes the *p*-nitrophenylserine ester hydrochloride began to separate. After 10 minutes' refluxing the mixture was cooled and stored in the ice-chest overnight, to give 72·5 g. of product, m. p. 176—179° (decomp.), a further 5 g. being obtained from the mother-liquors on concentration. The crude hydrochloride (133·5 g.) was stirred for 3 hours at room temperature in N-sodium hydroxide (913 ml.)–alcohol (270 ml.). Neutralisation of the resulting yellow solution with N-hydrochloric acid gave *erythro*-β-*p*-nitrophenylserine as a cream-coloured powder (*ca.* 100%), m. p. 187—188° (decomp.) after recrystallisation from water and drying (P_2O_5) at 80°/0·5 mm. (Found: C, 47·9; H, 5·1; N, 12·2. Calc. for $C_9H_{10}O_5N_2$: C, 47·8; H, 4·4; N, 12·4%).

In another experiment the filtrates at each stage were subjected to the same reactions as the corresponding isolated solids, the *p*-nitrobenzaldehyde liberated on acid treatment of the Schiff's base being removed before the final alkaline hydrolysis by evaporation and extraction of the residue with benzene and ether. Aqueous solutions (0·3%) from each crop of solid amino-acid, together with the corresponding mother-liquors, were compared with pure specimens of the two *p*-nitrophenylserines by partition chromatography on Whatman No. 1 paper with butanol–formic acid–water (10 : 1 : 10). Results indicated a 50% overall yield of pure *erythro*-*p*-nitrophenylserine (R_F 0·48) and a further 8% apparently consisting mainly of the *erythro*-compound but also containing a little of the *threo*-form (R_F 0·41); the mother-liquors appeared to contain substantial amounts of both forms and also some glycine (R_F 0·12). In an experiment without triethylamine, *i.e.*, essentially as described by Bergmann *et al.* (*loc. cit.*), the chromatographic results were qualitatively similar but the total overall yield of solid amino-acid was only 9%.

N-*Acetyl*-erythro-p-*nitrophenylserine*.—*erythro*-*p*-Nitrophenylserine was acetylated as described for *threo*-phenylserine, the *derivative* crystallising from water as pale yellow platelets, m. p. 170° (decomp.) (Found: C, 47·5; H, 4·7; N, 10·3. $C_{11}H_{12}O_6N_2,0{\cdot}5H_2O$ requires C, 47·6; H, 4·7; N, 10·1%). The m. p. and analysis were unchanged when the compound was dried (P_2O_5) at 80°/0·2 mm. for 3 hours. This derivative depressed the m. p. of the *threo*-isomer.

2-*Methyl*-4-p-*nitrobenzylidene*-5-*oxazolone*.—*p*-Nitrobenzaldehyde (2 g.), aceturic acid (1·83 g.), and fused sodium acetate (0·87 g.) in acetic anhydride (5 ml.) were heated on the water-bath for 1 hour. After cooling, the resulting *oxazolone* (2·2 g.) was washed first with 50% aqueous alcohol and then with ether and crystallised from alcohol–acetone (charcoal) as bright yellow needles, m. p. 186—187° (Found: C, 56·9; H, 3·9; N, 12·2. $C_{11}H_8O_4N_2$ requires C, 56·9; H, 3·5; N, 12·1%). The same compound was formed when either form of *N*-acetyl-*p*-nitrophenylserine was heated for a few minutes with acetic anhydride.

threo-p-*Nitrophenylserine Ethyl Ester Hydrochloride*.—A suspension of *threo-p*-nitrophenylserine (7 g.) in ethanol (100 ml.) was refluxed in a stream of dry hydrogen chloride for 4 hours. Evaporation of the clear yellow solution *in vacuo* left a syrup which on treatment with ethyl acetate and ether yielded a crystalline deliquescent solid (5·80 g.), crystallising from acetonitrile as non-deliquescent needles of the *hydrochloride*, m. p. 157—159° (softening at 154°) (Found : C, 45·3; H, 5·0; N, 9·65; Cl, 12·2. $C_{11}H_{15}O_5N_2Cl$ requires C, 45·4; H, 5·2; N, 9·6; Cl, 12·2%). The free ethyl ester was liberated by treating an ice-cold suspension of the hydrochloride with the calculated quantity of potassium carbonate solution, and crystallised from benzene as needles, m. p. 129—130° (Found : C, 52·0; H, 5·6; N, 11·3. Calc. for $C_{11}H_{14}O_5N_2$: C, 52·0; H, 5·55; N, 11·0%). The *erythro*-ester, similarly prepared and purified, formed needles, m. p. 114—115° (Found : C, 52·1; H, 5·4; N, 11·2%). The m. p.s of these esters depend markedly on the rate of heating, which may account for discrepancies in the literature.

N-*Acetyl*-threo-p-*nitrophenylserine Ethyl Ester*.—A solution of the *threo*-ester hydrochloride (2·91 g.) in ice-water (30 c.c.) was treated with acetic anhydride (2·5 ml.), followed by a solution of sodium acetate trihydrate (5 g.) in water (10 ml.), shaken at room temperature overnight, acidified with hydrochloric acid, and cooled to 0°, and the crude product collected (2·56 g.). N-*Acetyl*-threo-p-*nitrophenylserine ethyl ester* crystallised from 50% aqueous alcohol in needles, m. p. 182—184° (softening at 177°) (Found : C, 52·9; H, 5·4; N, 9·7. $C_{13}H_{16}O_6N_2$ requires C, 52·7; H, 5·4; N, 9·5%). The *erythro-N*-acetyl-ester, prepared similarly and crystallised from water, formed needles, m. p. 148—149° (softening at 144°) (Found : C, 52·7; H, 5·7; N, 9·2%). Moersch *et al.* (*loc. cit.*) give m. p. 158—159°.

threo-2-*Acetamido*-1-p-*nitrophenylpropane*-1 : 3-*diol*.—Lithium aluminium hydride (0·48 g.) in dry ether (50 ml.) was added during 2 hours to a stirred solution of *N*-acetyl-*threo-p*-nitrophenylserine ethyl ester (1·48 g.) in dry dioxan (75 ml.), then stirred for a further 2·5 hours, treated successively with water (5 ml.) and 5N-hydrochloric acid (5 ml.), and evaporated. An aqueous solution (20 ml.) of the residue was extracted with ethyl acetate (4 × 50 ml.). The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo*, leaving a gum which on trituration with ethyl acetate yielded a pale brownish-yellow solid (0·29 g.). Recrystallisation from acetone gave a practically colourless powder, m. p. 165—167° not depressed by admixture with an authentic specimen of *threo*-2-acetamido-1-*p*-nitrophenylpropane-1 : 3-diol prepared by Long and Troutman's method (*J. Amer. Chem. Soc.*, 1949, **71**, 2473) (Found : C, 52·0; H, 5·6; N, 11·0. Calc. for $C_{11}H_{14}O_5N_2$: C, 52·0; H, 5·55; N, 11·0%).

erythro-2-Acetamido-1-*p*-nitrophenylpropane-1 : 3-diol, similarly prepared from the *erythro*-ester in 11% yield and crystallised from acetone, had m. p. 191—193° (Long and Troutman give m. p. 195°) (Found : C, 52·5; H, 5·8; N, 10·9%).

N-p-*Nitrobenzylidene*-threo-p-*nitrophenylserine Ethyl Ester*.—To a hot solution of *threo-p*-nitrophenylserine ethyl ester (10 g.) in chloroform (500 ml.) was added *p*-nitrobenzaldehyde (6 g.) and anhydrous sodium sulphate (5 g.). After 3 days at room temperature the filtered mixture on concentration *in vacuo* and trituration with ether at low temperature yielded N-p-*nitrobenzylidene*-threo-p-*nitrophenylserine ethyl ester* as a white powder (12·25 g.). This was best purified by repeated crystallisation from dry ether, forming needles, m.p. 121—121·5°, absorption max. at 2690 Å ($E^{1\%}_{1\,cm.}$ 621 in $CHCl_3$) (Found : C, 56·0; H, 4·8; N, 11·2. $C_{18}H_{17}O_7N_3$ requires C, 55·8; H, 4·4; N, 10·85%).

The *erythro*-Schiff's base, similarly prepared, had m. p. 146—147°, undepressed by admixture with the product from *p*-nitrobenzaldehyde and glycine ester; it had an absorption max. at 2700 Å ($E^{1\%}_{1\,cm.}$ 635 in $CHCl_3$).

erythro-p-*Aminophenylserine*.—*erythro-p*-Nitrophenylserine (30 g.) in 1·37N-hydrochloric acid (200 ml.) and alcohol (200 ml.) was hydrogenated at ordinary temperature and pressure on Adams's catalyst, absorption being complete in 5 hours. The resulting pale yellow solution was filtered into a little water containing a trace of sodium dithionite and concentrated under reduced pressure under hydrogen. The syrupy residue was treated with a little water and the concentration twice repeated. The final residue was taken up into water (70 ml.) containing a little sodium dithionite and neutralised to pH 7 with ammonia, to precipitate *p*-aminophenylserine (22·7 g.). Recrystallisation from aqueous alcohol gave a cream-coloured powder, m. p. 205—207° (decomp.) (Found : C, 50·6; H, 6·9; N, 13·0. Calc. for $C_9H_{12}O_3N_2,H_2O$: C, 50·5; H, 6·6; N, 13·1%).

threo-p-*Aminophenylserine*.—*threo-p*-Nitrophenylserine (30 g.) was reduced and worked up as described above, to give 73% of threo-p-*aminophenylserine*, m. p. 205° (decomp.) (rapid heating from 180°), from aqueous alcohol (Found : C, 50·0; H, 6·5; N, 13·0%).

N^1-*Acetyl*-threo-p-*aminophenylserine*.—A solution of *N*-acetyl-*threo-p*-nitrophenylserine

(3·23 g.) in alcohol (100 ml.) was hydrogenated at ordinary temperature and pressure on Adams's catalyst, some solid separating towards the end of the reduction which was complete in 1 hour. The mixture was heated with further alcohol (50 ml.) and the resulting solution filtered. On cooling of the filtrate N^1-*acetyl*-threo-p-*aminophenylserine* separated and a further crop was obtained from the concentrated mother-liquors (charcoal). The product (2·08 g.) had m. p. 124—125°, not increased by recrystallisation from alcohol (Found: C, 53·5; H, 6·4; N, 11·8. $C_{11}H_{14}O_4N_2,0{\cdot}5H_2O$ requires C, 53·4; H, 6·1; N, 11·3%).

erythro-p-*Hydroxyphenylserine.*—A solution of *erythro-p*-aminophenylserine (4·5 g.) in a mixture of sulphuric acid (4·9 ml.) and water (35 ml.) was kept at −5° to 0° whilst a solution of sodium nitrite (1·44 g.) in water (5 ml.) was added dropwise with stirring during 20 minutes. After a further 10 minutes' stirring below 0° the solution was heated on the steam-bath for 10 minutes (negative diazo-test), kept for 1 hour at room temperature, clarified with charcoal, and neutralised to pH 7 with ammonia. erythro-p-*Hydroxyphenylserine* separated immediately as a cream-coloured powder (2·67 g.) and a further 0·48 g. was obtained from the mother-liquor. The product, crystallised from 30% acetic acid, had m. p. 212° (decomp.) after becoming brown at 200° (Found, after drying over P_2O_5 at 100°/0·5 mm.: C, 54·7; H, 5·9; N, 7·0. $C_9H_{11}O_4N$ requires C, 54·8; H, 5·6; N, 7·1%).

threo-p-*Hydroxyphenylserine.*—*threo-p*-Aminophenylserine (9·89 g.) was diazotised, etc., essentially as described for the *erythro*-compound. The resulting brown solution on neutralisation with ammonia and refrigeration gave 1·33 g. of brown intractable material which was discarded. The residual liquor was concentrated *in vacuo* to yield a pale brown solid which was dried, washed with hot alcohol, and then treated with successive small quantities of water (37 ml. in all) till free from sulphate. The residual pale yellow powder threo-p-*hydroxyphenylserine* was purified by adding an equal volume of alcohol to its solution in hot water. The product separated slowly on refrigeration as a pale yellow powder, m. p. 188° (decomp.). It was dried (P_2O_5) at 100°/0·5 mm. (Found: C, 54·8; H, 5·9; N, 7·0%).

An attempt to convert N^1-acetyl-*threo-p*-aminophenylserine into the *N*-acetyl-*p*-hydroxy-compound by a similar method gave intractable material.

No clear separation of *threo-* and *erythro-p*-hydroxyphenylserine could be obtained by paper partition chromatography. However, with water-saturated *n*-butanol containing 10% of diethylamine as the mobile phase *erythro-p*-hydroxyphenylserine gave a compact spot after development with ninhydrin, whereas the *threo*-isomer gave a long diffuse spot. The *p*-hydroxyphenylserine prepared by Rosenmund and Dornsaft's method (*loc. cit.*) gave a compact spot, indicating it to be the *erythro*-form.

erythro-β-p-*Chlorophenylserine.*—*erythro-p*-Aminophenylserine (4·5 g.) in hydrochloric acid (12 ml.) and water (5 ml.) was diazotised with sodium nitrite (1·44 g.) in water (4·5 ml.), and the resulting mixture poured into a solution of cuprous chloride in concentrated hydrochloric acid (9 ml.) at 0° (from copper sulphate, 6·55 g.). After 1 hour's stirring and storage for a further 1·5 hours, the mixture was heated to 70° for 5 minutes and then diluted with hot water (50 ml.). Copper was removed by hydrogen sulphide, and the filtered solution concentrated several times, with the addition of water, under reduced pressure. The residue was dissolved in hot water (20 ml.) (charcoal) and neutralised to pH 7 with triethylamine while still hot. After cooling to 0°, the precipitated erythro-p-*chlorophenylserine* (3·47 g.) was collected and crystallised from aqueous alcohol, to give a colourless powder, m. p. 178° (decomp.) after becoming brown at 170° (Found, after drying over P_2O_5 at 100°/0·5 mm.: C, 47·9; H, 5·3; N, 6·5; Cl, 15·8. $C_9H_{10}O_3NCl,0{\cdot}5H_2O$ requires C, 48·1; H, 4·9; N, 6·3; Cl, 15·8%).

erythro-p-Chlorophenylserine was acetylated as described for *threo*-phenylserine, the *acetyl* derivative separating from water as a colourless powder, m. p. 165° (decomp.) (Found: N, 5·4; Cl, 13·8. $C_{11}H_{12}O_4NCl$ requires N, 5·4; Cl, 13·8%).

N-*Acetyl*-threo-β-p-*chlorophenylserine.*—N^1-Acetyl-*threo-p*-aminophenylserine (5 g.) was diazotised, etc., essentially as described for the preparation of *erythro-p*-chlorophenylserine. The reaction mixture was cooled at room temperature and the precipitated N-*acetyl* derivative (2·0 g.) washed with 5N-hydrochloric acid and then with water. A further 0·5 g. was obtained by extracting the mother-liquors with ethyl acetate. Recrystallisation from water gave a powder, m. p. 176° (decomp.), depressed on admixture with *N*-acetyl-*erythro*-β-*p*-chlorophenylserine (Found: C, 51·0; H, 4·4; N, 5·9; Cl, 13·8. $C_{11}H_{12}O_4NCl$ requires C, 51·3; H, 4·7; N, 5·4; Cl, 13·8%).

threo-β-p-*Chlorophenylserine.*—(a) *From the above* N-*acetyl derivative.* This derivative (1·03 g.) was heated under reflux with 50% (v/v) hydrochloric acid (15 ml.) for 5·5 hours, and the mixture cooled and filtered. The filtrate was concentrated under reduced pressure several times with

water; the final residue was dissolved in water (2 ml.), alcohol (2 ml.) added, and the mixture heated and then adjusted to pH 7 with triethylamine. After refrigeration overnight the precipitated threo-p-*chlorophenylserine* (0·47 g.) was collected and crystallised from aqueous alcohol, then having m. p. 175—176° (decomp.) (Found: N, 6·7. $C_9H_{10}O_3NCl$ requires N, 6·5%).

(b) *From* p-*chlorobenzaldehyde and glycine.* To a mixture of *p*-chlorobenzaldehyde (7·03 g.) and glycine (1·88 g.) in 50% aqueous alcohol (20 ml.) a solution of sodium hydroxide (3·5 g.) in water (10 ml.) was added during 5 minutes, with rapid shaking which was continued for 1 hour, and the resulting suspension was then kept overnight at room temperature. The product was filtered off, washed with alcohol, then suspended in water (50 ml.), acidified to pH 4 to 5 with acetic acid, and shaken with ether. *threo*-β-*p*-Chlorophenylserine (1·73 g.) was collected and washed with water and ether, the aqueous layer of the filtrate affording a further 1·41 g. on concentration and addition of alcohol. Recrystallisation from water (charcoal) gave a powder, m. p. 179° (decomp.) (Found: C, 49·9; H, 4·6; N, 6·2. Calc. for $C_9H_{10}O_3NCl$: C, 50·1; H, 4·6; N, 6·5%).

The acetyl derivative of this product had m. p. 174—175° (decomp.), undepressed on admixture with *N*-acetyl-*threo*-β-*p*-chlorophenylserine.

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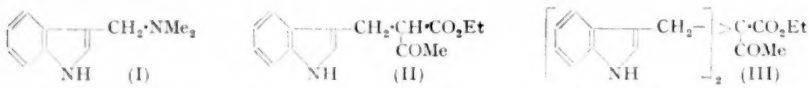
57. *New Syntheses of* DL-*Tryptophan. Part I. Syntheses from Ethyl α-Aceto-β-3-indolylpropionate and Ethyl α-Cyano-β-3-indolylpropionate.*

By D. O. Holland and J. H. C. Nayler.

Three new syntheses of tryptophan are described, two of which start from ethyl α-aceto-β-3-indolylpropionate and the third from ethyl α-cyano-β-3-indolylpropionate.

Numerous satisfactory syntheses of DL-tryptophan involve the condensation of gramine (I) or other 3-dialkylaminomethylindoles or their quaternary salts with such compounds as α-acylamino-acetoacetic, -cyanoacetic, or -malonic, nitroacetic, or nitromalonic esters, most of this work having been briefly reviewed by Rydon (*Ann. Reports*, 1949, **46**, 193; 1950, **47**, 175). Acetoacetic, cyanoacetic, and malonic ester undergo similar condensations (Snyder, Smith, and Stewart, *J. Amer. Chem. Soc.*, 1944, **66**, 200; Albertson, Archer, and Suter, U.S.P. 2,468,912) but the products, which lack a nitrogen-containing precursor of the amino-group, have not hitherto been utilised for the synthesis of tryptophan. The present paper records a number of attempts to convert condensation products of this second group into the amino-acid.

Ethyl α-aceto-β-3-indolylpropionate (II), previously obtained as a crude oil (Snyder, *et al.*; Albertson *et al., locc. cit.*), has now been prepared more conveniently by treating gramine methosulphate with ethyl sodioacetoacetate in alcohol at room temperature, the gramine methosulphate being produced *in situ* (Albertson, Archer, and Suter, *J. Amer. Chem. Soc.*, 1945, **67**, 36). An excess of ethyl acetoacetate must be used, otherwise the crude product contains substantial amounts of ethyl αα-di-(3-indolylmethyl)acetoacetate (III). The latter was formed in high yield on treatment of the sodio-derivative of (II) with gramine methosulphate.



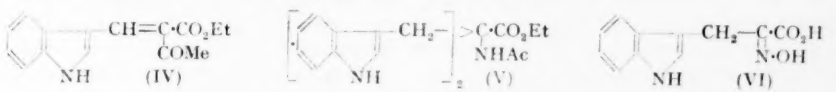
According to U.S.P. 2,468,912 hydrolysis of ethyl α-aceto-β-3-indolylpropionate (II) with hot concentrated sodium hydroxide solution gives β-3-indolylpropionic acid, but following

the prescribed method we obtained a high yield of 2-3′-indolylethyl methyl ketone and none of the acid.

We also examined the catalytic hydrogenation of ethyl α-3-indolylmethyleneacetoacetate (IV), formed by the condensation of ethyl α-ethoxymethyleneacetoacetate with indole. However, considerably more than the theoretical amount of hydrogen was absorbed and the oily product gave only a comparatively poor yield of 2-(3-indolyl)ethyl methyl ketone on hydrolysis.

Attempts to apply the Japp–Klingemann reaction using potassium benzenediazoate to ethyl α-aceto-β-3-indolylpropionate under essentially the conditions employed by Feofilaktov (*Compt. rend. Acad. Sci., U.R.S.S.*, 1939, **24**, 755) for the synthesis of a number of amino-acids were unsuccessful, yielding only tars and none of the required indole-3-pyruvic acid phenylhydrazone on subsequent hydrolysis. On the other hand, application of the Schmidt reaction with hydrazoic acid in the presence of concentrated sulphuric acid readily afforded *N*-acetyltryptophan ethyl ester in good yield. From impure specimens of ethyl α-aceto-β-3-indolylpropionate containing the disubstitution product (III), there was also obtained the corresponding ethyl αα-di-(3-indolylmethyl)aceturate (V). Hydrolysis of *N*-acetyltryptophan ester with aqueous sodium hydroxide at room temperature afforded *N*-acetyltryptophan, and prolonged heating gave the free amino-acid in 62% overall yield from indole.

Ethyl α-aceto-β-3-indolylpropionate (II) was also converted into tryptophan by way of β-3-indolyl-α-oximinopropionic acid (VI). This acid, first synthesised from indole-3-pyruvic acid and hydroxylamine by Bauguess and Berg (*J. Biol. Chem.*, 1934, **104**, 675), was readily prepared in moderate yield by the nitrosation of ethyl α-aceto-β-3-indolylpropionate (II) by one of the procedures described by Barry and Hartung (*J. Org. Chem.*, 1947, **12**, 460). The oximino-ester was hydrolysed *in situ* directly to the acid by brief heating with alkali, slow hydrolysis in the cold giving only a very crude product. Bauguess and Berg (*loc. cit.*) described the conversion of (VI) into tryptophan by hydrogenation in alcohol over Raney nickel at atmospheric temperature and pressure, but we found reduction to be more satisfactory in dilute aqueous ammonia at about 60°.



In view of the findings of Barry and Hartung (*loc. cit.*) it was expected that better yields of the oximino-acid (VI) might be obtained by nitrosation of diethyl (3-indolylmethyl)malonate (VII; R = Et) or the corresponding acid (VII; R = H). However, reaction of the ester with *n*-butyl nitrite in the presence of sodium ethoxide gave no oximino-acid, whilst reaction of either the ester or the acid in the presence of dry hydrogen chloride gave only tars.

Hofmann and Curtius reactions with ethyl α-cyano-β-3-indolylpropionate (VIII; R = Et) were next investigated. The amide from (VIII) with sodium hypobromite or hypochlorite gave neither the amino-nitrile nor the hydantoin (which is known). The

acid (VIII; R = H) was converted into the acid-amide (IX) but this with sodium hypobromite also gave no tryptophan. The failure of the Hofmann reaction in these two cases is not surprising in view of the known sensitiveness of the indole ring to hypohalites. By contrast, the Curtius reaction provided a satisfactory route from (VIII; R = Et) to tryptophan, hydrolysis of the urethane (X) being accomplished by prolonged heating with hydrochloric and acetic acids. The use of a mixture of hydrochloric and formic acids, which

has been reported by Gagnon and Boivin (*Canad. J. Res.*, 1948, **26**, *B*, 503) to be advantageous for other amino-acids, was unsuccessful in the present case, the mixture developing an intense purple colour and yielding much tar.

Experimental

M. p.s are uncorrected.

Ethyl α-Aceto-β-3-indolylpropionate (II).—To a solution of sodium (2·3 g.) in ethanol (80 ml.) were added ethyl acetoacetate (25·2 ml., 2 mols.) and gramine (17·4 g.). Methyl sulphate (19·2 ml.) was run in during 30 minutes with stirring and cooling to 10—20°, the gramine rapidly dissolving. After a further 4 hours' stirring at ordinary temperature the mixture was evaporated under reduced pressure and the sticky residue treated with chloroform (120 ml.) and water (80 ml.). When dissolution was complete the organic phase was washed with water and dried (Na_2SO_4), and chloroform and excess of ethyl acetoacetate were removed *in vacuo* to leave the crude product as an amber syrup (24·5 g., 95%). A specimen for analysis was obtained by distillation at 150°/0·0005 mm. (Found: C, 69·9; H, 6·5; N, 5·5. Calc. for $C_{15}H_{17}O_3N$: C, 69·5; H, 6·6; N, 5·4%).

The solvated **2** : **4**-*dinitrophenylhydrazone* (from ethyl acetate) had m. p. 129—131° (softening 127°) (Found: C, 57·0; H, 5·3, N, 14·3, 14·7. $C_{21}H_{21}O_6N_5,0{\cdot}5C_4H_8O_2$ requires C, 57·1; H, 5·2; N, 14·5%). Complete removal of solvent required 28 hours' heating at 100°/0·2 mm. and left an orange powder, m. p. 133—135° (Snyder, Smith, and Stewart, *loc. cit.*, give m. p. 133·5°) (Found: C, 57·3; H, 4·6; N, 16·2; loss, 9·1. Calc. for $C_{21}H_{21}O_6N_5$: C, 57·4; H, 4·8; N, 15·9; loss, 9·1%).

Ethyl αα-Di-(3-indolylmethyl)acetoacetate (III).—(*a*) When the preparation of ethyl α-aceto-β-3-indolylpropionate was carried out as described above but with only 1 mol. of ethyl acetoacetate a good yield of crude syrup resulted but this was found to be only very impure (II). Cautious dilution of its ethereal solution with light petroleum precipitated a pale solid (generally about 20% by wt. of the whole) which on recrystallisation from ether–light petroleum afforded *ethyl αα-di-(3-indolylmethyl)acetoacetate*, m. p. 143—144° (Found: C, 73·8; H, 6·4; N, 7·6. $C_{24}H_{24}O_3N_2$ requires C, 74·2; H, 6·2; N, 7·2%).

(*b*) Ethyl α-aceto-β-3-indolylpropionate (II) (6·47 g.) was dissolved in a solution of sodium (0·58 g.) in ethanol (20 ml.). Gramine (4·35 g.) was added and methyl sulphate (4·8 ml.) run in with stirring during 25 minutes. After a further 4 hours' stirring at ordinary temperature the mixture was evaporated *in vacuo* and the solid residue treated with chloroform (60 ml.) and water (35 ml.). Undissolved material, m. p. 141—145° (4·46 g.), was collected and the organic phase of the filtrate washed, dried, and evaporated *in vacuo*. The residual gum yielded a further quantity of solid (m. p. 136—139°) on trituration with toluene, the total yield of ethyl αα-di-(3-indolylmethyl)acetoacetate undepressed on admixture with material from (*a*) being 7·94 g. (82%). The **2** : **4**-*dinitrophenylhydrazone* separated from ethyl acetate as an orange-yellow powder, m. p. 204—206° (decomp.) (Found: C, 63·2; H, 5·3; N, 14·4. $C_{30}H_{28}O_6N_6$ requires C, 63·4; H, 5·0; N, 14·8%).

Hydrolysis of Ethyl α-Aceto-β-3-indolylpropionate.—The propionate (II) (5·02 g.) was heated for 2 hours on the steam-bath with sodium hydroxide (18 g.) in water (33 ml.) as described in U.S.P. 2,468,912 but much oil remained undissolved. On cooling, the oil solidified and the resulting solid was collected and thoroughly washed with water to leave a fawn powder (3·42 g.), m. p. 87—89°. Thorough extraction of the acidified filtrate with ether failed to yield β-3-indolylpropionic acid. Recrystallisation of the above-mentioned neutral solid from light petroleum gave needles of *2-3′-indolylethyl methyl ketone*, m. p. 93° (Found: C, 76·4; H, 6·7; N, 7·7. $C_{12}H_{13}ON$ requires C, 77·0; H, 7·0; N, 7·5%). The **2** : **4**-*dinitrophenylhydrazone* crystallised from dioxan–alcohol in small red needles, m. p. 209—210° (Found: C, 58·5; H, 4·8; N, 19·0. $C_{18}H_{17}O_4N_5$ requires C, 58·8; H, 4·7; N, 19·1%).

Ethyl α-3-Indolylmethyleneacetoacetate (IV).—A solution of ethyl α-ethoxymethyleneacetoacetate (Claisen, *Annalen*, 1897, **297**, 16) (39·0 g.) and indole (24·5 g.) in acetic acid (80 ml.) containing acetic anhydride (20 ml.) was heated on the steam-bath for 2 hours and the solvents were removed *in vacuo*. The residual sticky yellow-brown solid was washed with ice-cold ether to leave a yellow powder, m. p. 132—134°, concentration of the ethereal washings affording a small second crop. The combined solids (32·5 g.) crystallised first from ethanol and then from benzene, to give *ethyl α-3-indolylmethyleneacetoacetate* as yellow needles, m. p. 135—136° (slow heating from 115°) (Found: C, 70·0; H, 5·8; N, 5·35. $C_{15}H_{15}O_3N$ requires C, 70·0; H, 5·9; N, 5·45%).

Reduction of Ethyl α-3-*Indolylmethyleneacetoacetate.*—A solution of the ester (IV) (15·0 g.) in alcohol (600 ml.) was hydrogenated at ordinary temperature and pressure over Adams's platinum oxide (0·4 g. added in two lots). Uptake of hydrogen ceased after about 24 hours, approx. 1·5 mols. having been consumed. After removal of the catalyst the pale filtrate and washings were evaporated to leave an amber-coloured syrup of impure ethyl α-aceto-β-3-indolylpropionate (II). The product was characterised as the 2 : 4-dinitrophenylhydrazone and by hydrolysis to 2-3′-indolylethyl methyl ketone, but the yields of these derivatives were not good.

Schmidt Reaction on Ethyl α-*Aceto*-β-3-*indolylpropionate.*—Ethyl α-aceto-β-3-indolylpropionate (14·5 g.) in dry chloroform (60 ml.) was treated with hydrazoic acid in chloroform (46·6 ml. of 5·14% w/v solution), and the mixture was added dropwise during 1 hour to a vigorously stirred mixture of concentrated sulphuric acid (40 ml.) and chloroform (40 ml.) kept at −5° to 0°. The mixture was then stirred for 30 minutes at the same temperature and then poured on about 300 g. of ice. The aqueous phase was extracted with chloroform (2 × 100 ml.). The combined chloroform solutions were washed, dried (Na_2SO_4), and evaporated *in vacuo* and the residual red gum was triturated with a little ether, to yield crude *N*-acetyltryptophan ethyl ester as a cream-coloured powder (12·7 g., 83%), m. p. 130—133°. A specimen recrystallised from 50% aqueous alcohol formed plates, m. p. 131·5—132·5° (Albertson, Tullar, King, Fishburn, and Archer, *J. Amer. Chem. Soc.*, 1948, **70**, 1150, give m. p. 133·5—135·5°) (Found : C, 65·5; H, 6·9; N, 10·5. Calc. for $C_{15}H_{18}O_3N_2$: C, 65·7; H, 6·6; 10·2%).

In one early experiment a specimen of ethyl α-aceto-β-3-indolylpropionate prepared from gramine methosulphate and only 1 mol. of ethyl acetoacetate and consequently containing a substantial amount of ethyl αα-di-(3-indolylmethyl)acetoacetate (III), gave, in addition to the normal product, *ethyl* αα-*di*-(3-*indolylmethyl*)*aceturate* (V), separated therefrom by reason of its insolubility in hot 50% aqueous alcohol and crystallising from acetone–water or acetonitrile in needles, m. p. 244—245° (Found : C, 71·6; H, 6·4; N, 10·4. $C_{24}H_{25}O_3N_3$ requires C, 71·5; H, 6·3; N, 10·4%).

Hydrolysis of N-*Acetyltryptophan Ethyl Ester.*—(*a*) A suspension of *N*-acetyltryptophan ethyl ester (1 g.) in 10% aqueous sodium hydroxide (5 ml.) was shaken overnight at room temperature and the solution acidified, to yield crude *N*-acetyltryptophan (0·79 g.), m. p. 201—203°, raised to 206° by recrystallisation from dilute aqueous alcohol (Found : C, 63·2; H, 5·6; N, 11·6. Calc. for $C_{13}H_{14}O_3N_2$: C, 63·4; H, 5·7; N, 11·4%).

(*b*) *N*-Acetyltryptophan ethyl ester (10 g.) was refluxed for 21 hours with 10% aqueous sodium hydroxide (100 ml.) and the resulting hot orange solution decolorised with charcoal, treated with acetic acid (35 ml.), and stored in the refrigerator for 48 hours. The solid was collected, washed with water, dried, and recrystallised from acetic acid, a little insoluble matter being discarded. Further purification was effected by dissolution in hot 33% aqueous alcohol (190 ml.) containing sodium hydroxide (2·5 g.) and addition of acetic acid to pH 5—6, pure tryptophan separating on cooling in plates (6·26 g., 84%), m. p. 285—287° (decomp.) [control m. p. 283—287° (decomp.)] not raised by further crystallisation from 33% aqueous alcohol (Found : C, 64·8; H, 6·0; N, 13·7. Calc. for $C_{11}H_{12}O_2N_2$: C, 64·7; H, 5·9; N, 13·7%).

β-3-*Indolyl*-α-*oximinopropionic Acid.*—(*a*) Ethyl α-aceto-β-3-indolylpropionate (4·32 g.) was dissolved in a solution of sodium (0·38 g.) in dry ethanol (16 ml.) and to the stirred solution a mixture of *n*-butyl nitrite (1·9 ml.) and ethanol (8 ml.) was added dropwise during 30 minutes at −5° to 0°. After a further 3 hours at 0° the dark solution was poured on crushed ice (about 100 g.) containing 5 ml. of concentrated hydrochloric acid, and the red-brown gum was extracted into ether. After being washed with a little water the ethereal solution was extracted with 10% aqueous sodium hydroxide (3 × 10 ml.), and the red alkaline solution heated on the steam-bath for 15 minutes. The cooled solution was acidified below 5°, the crude oximino-acid separating as a light brown powder. Partial purification was effected by dissolution in sodium hydrogen carbonate solution, filtration from a little insoluble material, and reprecipitation with acid, to give a fawn-coloured powder (2·16 g., 59%), m. p. 144° (decomp.). This material was suitable for reduction to tryptophan, but for analysis a specimen was further purified by repeated recrystallisation from ether–light petroleum, to m. p. 154° (decomp.) (Found : C, 60·5; H, 4·7; N, 12·4. Calc. for $C_{11}H_{10}O_3N_2$: C, 60·5; H, 4·6; N, 12·8%). Bauguess and Berg (*loc. cit.*) give m. p. indef., >175°.

Other methods of nitrosation (cf. Barry and Hartung, *loc. cit.*) failed.

(*b*) A solution of indole-3-pyruvic acid (0·14 g.), sodium hydrogen carbonate (0·8 g.), and hydroxylamine hydrochloride (0·25 g.) in water (8 ml.) was kept at ordinary temperature for 18 hours, then filtered, and the filtrate acidified. The precipitate was almost pure β-3-indolyl-α-

oximinopropionic acid, m. p. 153° (decomp.) (0·13 g.). Recrystallisation from ether–light petroleum gave very pale fawn-coloured crystals, m. p. 155° (decomp.) not depressed on admixture with the product from (*a*) (Found : N, 12·9%).

Reduction of β-3-*Indolyl-α-oximinopropionic Acid.*—A solution of the oximino-acid (0·5 g.) in water (50 ml.) containing aqueous ammonia (*d* 0·88, 2 ml.) was hydrogenated at 60—65°/approx. 1 atm. over Raney nickel (about 0·5 g.), uptake of hydrogen ceasing after 4 hours when approx. 1·8 mols. had been consumed. Filtration and evaporation *in vacuo* gave crude tryptophan as a nearly white powder (0·34 g., 72%), m. p. 261—264° (decomp.), raised to 279—280° (decomp.) [control, m. p. 279—280° (decomp.)] by recrystallisation from acetic acid and then from 33% aqueous alcohol.

Ethyl α-Cyano-β-3-indolylpropionate (VIII; R = Et).—This ester was obtained almost quantitatively as a crude red oil by the action of gramine methiodide on ethyl sodiocyanoacetate as described by Snyder, Smith, and Stewart (*loc. cit.*) except that xylene was substituted for butyl ether as solvent.

α-Cyano-β-3-indolylpropionamide.—A solution of crude α-cyano-ester (24·7 g.) in methanol (300 ml.) was saturated with ammonia at 0° and set aside in a stoppered vessel at room temperature for 4 days. Concentration *in vacuo* to about 80 ml. and cooling to 0° gave a first crop (7·62 g.) of white powder, m. p. 170—172°; evaporation of the filtrate and trituration of the residual syrup with ether yielded a sticky solid which on recrystallisation from aqueous alcohol gave a further 2·04 g., m. p. 169—170°. Further crystallisation from acetic acid or aqueous alcohol gave pure *α-cyano-β-3-indolylpropionamide*, plates, m. p. 173—174° (Found: C, 67·7; H, 5·5; N, 20·1. $C_{12}H_{11}ON_3$ requires C, 67·6; H, 5·2; N, 19·7%).

α-Cyano-β-3-indolylpropionic Acid (VIII; R = H).—Crude ethyl α-cyano-β-3-indolylpropionate (11·65 g.) was refluxed for 1 hour with one equiv. of aqueous alcoholic potassium hydroxide. The solution was then evaporated *in vacuo*, the residue dissolved in hot water, decolorised with charcoal, and the cooled light red filtrate acidified with hydrochloric acid. The red oil which separated was removed in ether and the dried extracts were evaporated to a syrup which was dissolved in boiling chloroform (100 ml.) and concentrated to about 30 ml. On cooling, *α-cyano-β-3-indolylpropionic acid* (3·78 g.) was obtained as colourless needles, m. p. 142—144°, after further crystallisation from chloroform (Found : C, 67·2; H, 4·8; N, 13·3. $C_{12}H_{10}O_2N_2$ requires C, 67·3; H, 4·7; N, 13·1%).

α-Carbamyl-β-3-indolylpropionic Acid (IX).—A solution of the α-cyano-acid (1 g.) in concentrated sulphuric acid (7 ml.) was set aside overnight at room temperature, then poured on crushed ice, and the sticky precipitate extracted with ethyl acetate (3 × 50 ml.). The dried extracts were concentrated to about 30 ml. and diluted with chloroform (70 ml.) to yield, after storage in the refrigerator overnight, 0·99 g. of crude pink solid, m. p. 151° (decomp.) (softening and shrinking from 144°). *α-Carbamyl-β-3-indolylpropionic acid* was purified only with some difficulty, by dissolution in hot ethyl acetate (charcoal), concentration to a small volume, dilution with chloroform, and refrigeration. It formed a colourless microcrystalline powder, m. p. 151° (decomp.) (Found : C, 62·5; H, 5·4; N, 12·6. $C_{12}H_{12}O_3N_2$ requires C, 62·0; H, 5·2; N, 12·1%).

α-Cyano-β-3-indolylpropionhydrazide.—A mixture of crude ethyl α-cyano-β-3-indolylpropionate (15·84 g.), 85% hydrazine hydrate (4·1 g.), and ethanol (20 ml.) was heated gently to effect solution and then refluxed for 1 hour. The clear orange solution was decanted from a trace of gum and kept in the refrigerator for 2 days. A colourless solid (7·44 g.) slowly separated. Concentration of the filtrate gave a small second crop, the total yield of solid, m. p. 144—147°, being 7·92 g. (53%). The *hydrazide* crystallised from alcohol in needles, m. p. 149—150° (Found : C, 62·9; H, 5·3; N, 24·8. $C_{12}H_{12}ON_4$ requires C, 63·1; H, 5·3; N, 24·6%).

Ethyl 1-*Cyano*-2-3′-*indolylethylcarbamate* (X).—Sodium nitrite (2·08 g.) in water (10 ml.) was added during 5 minutes with vigorous stirring to a cooled mixture of ether (100 ml.) and a solution of the hydrazide (4·56 g.) in 5N-hydrochloric acid (40 ml.), at −10° to 0°. The layers were separated immediately and the ethereal solution was washed with water and aqueous sodium hydrogen carbonate and quickly dried ($CaCl_2$). Ethanol (100 ml.) was added and the ether was distilled off through a short column. The residual alcoholic solution was refluxed for 1 hour to complete the conversion of the azide into the urethane and then evaporated *in vacuo* to a brown gum. Trituration with toluene (cooling) yielded a crude light brown solid (3·55 g., 69%), m. p. 109—113°, crystallisation from aqueous alcohol (charcoal) affording needles of the *urethane* (X), m. p. 123—124° (Found : C, 65·3; H, 6·1; N, 16·5. $C_{14}H_{15}O_2N_3$ requires C, 65·3; H, 5·9; N, 16·3%).

Hydrolysis of the Urethane (X).—A solution of the urethane (1 g.) in acetic acid (8 ml.) and

concentrated hydrochloric acid (8 ml.) was refluxed for 72 hours, then evaporated *in vacuo*. The residue was dissolved in a little water, and the evaporation repeated twice more to remove the excess of acid. The residue was then dissolved in water (15 ml.) and heated with triethylamine (5 ml.) on the steam-bath for 30 mins., and the solution was evaporated to dryness *in vacuo*. The resulting sticky solid was thoroughly washed with alcohol to remove triethylamine hydrochloride, leaving crude tryptophan as a light brown powder (0·57 g., 67%), m. p. 273—275° (decomp.), which was purified as previously described.

The authors thank Mr. T. L. Hardy and Mr. D. L. Hatt for experimental assistance and the Directors of these laboratories for permission to publish.

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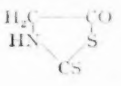
58. *New Syntheses of* DL-*Tryptophan. Part II.* A Synthesis from Indole and 2-Thio-5-thiazolidone.*

By D. O. HOLLAND and J. H. C. NAYLER.

A number of possible routes to tryptophan involving the use of 2-thio-5-thiazolidone have been examined, one of them succeeding in an indirect manner.

IN contrast to the numerous successful syntheses of DL-tryptophan in which 3-dialkylaminomethylindoles have been condensed with suitable acyclic intermediates (cf. Part I *), similar investigations with cyclic compounds have been confined to the observations by Howe, Zambito, Snyder, and Tishler (*J. Amer. Chem. Soc.*, 1945, **67**, 38) that gramine does not condense with hydantoin or diketopiperazine. Condensation of gramine with 2-thio-5-thiazolidone (I) was therefore investigated, this intermediate having proved of value for the synthesis of other amino-acids (Billimoria and Cook, " Studies in the Azole Series," Part XIX, *J.*, 1949, 2323, and other Parts in the series).

Attempts to condense gramine with 2-thio-5-thiazolidone in boiling toluene or xylene under nitrogen in the presence or absence of potassium carbonate (conditions similar to those used by Howe *et al.*, *loc. cit.*, for the condensation with acetamidomalonic ester) gave only gramine and an insoluble material which resembled the polymer produced when 2-thio-5-thiazolidone is heated in pyridine (Cook and Levy, *J.*, 1950, 637). Evidently 2-thio-5-thiazolidone is too sensitive to bases to undergo condensation with a tertiary amine such as gramine.



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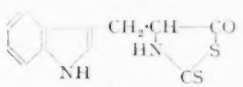

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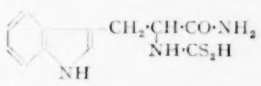


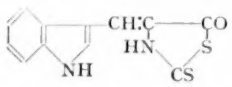
(III)

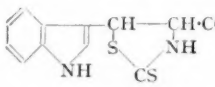
For comparison 4-3′-indolylmethyl-2-thio-5-thiazolidone (II) was prepared from DL-tryptophan amide and carbon disulphide. Attempts to isolate either the triethylamine or the tryptophan amide salts of the intermediate dithiocarbamic acid (III) were abandoned owing to their deliquescent nature and the reaction mixture was acidified to yield the thiazolidone directly. Although the ring closure of such intermediates is normally best carried out at 0°, this reaction proceeded satisfactorily only at a slightly higher temperature. The crude product obtained by acidification at or below room temperature had no reproducible melting point, could not be purified, gradually developed an odour of carbon disulphide, and when heated with picric acid in alcohol yielded a small amount of tryptophan amide picrate. These facts, supported by analytical results for the crude product, suggest that it may have been a mixture of the required thiazolidone (II) and the presumably unstable dithiocarbamic acid (III). 4-3′-Indolylmethyl-2-thio-5-thiazolidone was readily

* Part I, preceding paper.

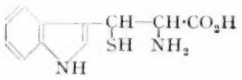
converted into tryptophan methyl ester hydrochloride by treatment with sodium methoxide followed by methanolic hydrogen chloride.

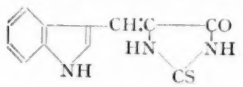
Next, 4-3′-indolylmethylene-2-thio-5-thiazolidone (IV) was prepared, without difficulty,

(IV) 

 (V)

from 2-thio-5-thiazolidone and indole-3-aldehyde, but reaction of indole with 4-ethoxymethylene-2-thio-5-thiazolidone (Cook, Heilbron, and Levy, *J.*, 1948, 201), afforded a more convenient route to it. Attempts to reduce (IV) to (II) by reagents such as zinc and acetic acid, zinc and dry hydrogen chloride in alcohol or dioxan, phosphorus and iodine in moist acetic acid, or sodium in liquid ammonia were unsuccessful. Then (IV) was converted into 5-3′-indolyl-2-thiothiazolidine-4-carboxylic acid (V) by the ring-turning reaction of Chatterjee, Cook, Heilbron, and Levy (*J.*, 1948, 1337), but attempts to prepare tryptophan therefrom by

(VI) 

 (VII)

way of β-3-indolylcysteine (VI) failed. Finally 4-3′-indolylmethylene-2-thio-5-thiazolidone (IV) was smoothly converted by concentrated aqueous ammonia into 5-3′-indolylmethylene-2-thiohydantoin (VII), the structure being proved by conversion into the known 5-3′-indolylmethylenehydantoin by chloroacetic acid in a modification of the general method of Johnson, Pfau, and Hodge (*J. Amer. Chem. Soc.*, 1912, **34**, 1041). [The action of ammonia on 4-alkylidene- or -arylidene-2-thio-5-thiazolidones may lead to 2-thiohydantoins or to ring-turning with the formation of 5-substituted-2-thiothiazolidine-4-carboxyamides, while in certain cases both products are formed (Cook, Hunter, and Pollock, *J.*, 1950, 1892); but (VII) was our sole product.] Since the hydantoin is readily converted into tryptophan by reduction and hydrolysis (cf. Elks, Elliot and Hems, *J.*, 1944, 629) the present reactions provide a novel, though circuitous, route to tryptophan.

Experimental

M.p.s are uncorrected

DL-*Tryptophan Methyl Ester Hydrochloride.*—DL-Tryptophan was esterified essentially by Abderhalden and Kempe's method (*Z. physiol. Chem.*, 1907, **52**, 207) for L-tryptophan. The product, obtained in 94% yield, crystallised from methanol–ether in needles, m. p. 225 (decomp.) (softening at 221°) (Found : C, 56·5; H, 6·2; N, 11·2; Cl, 13·7. Calc. for $C_{12}H_{15}O_2N_2Cl$: C, 56·6; H, 5·9; N, 11·0; Cl, 13·9%). Brenner, Sailer, and Kocher (*Helv. Chim. Acta*, 1948, **31**, 1908) give m. p. 216°, but it is not clear if this refers to a pure specimen.

DL-*Tryptophan Amide.*—DL-Tryptophan methyl ester hydrochloride (13 g.) was suspended in methanol (50 ml.), neutralised to phenolphthalein by sodium methoxide in methanol, and filtered to remove sodium chloride. The filtrate was cautiously saturated with gaseous ammonia, the temperature being kept at >0°, and, after 6 days at room temperature, evaporated *in vacuo*. Trituration with chloroform and crystallisation from this solvent afforded the *amide* (8·58 g.) as needles, m. p. 120—121° (Found : C, 63·5; H, 6·4; N, 20·4. $C_{11}H_{13}ON_3,0{\cdot}25H_2O$ requires C, 63·6; H, 6·55; N, 20·2%). Drying (P_2O_5) at 80°/0·4 mm. for 5 hours did not change the m. p. or analysis. Bauguess and Berg (*J. Biol. Chem.*, 1934, **106**, 615) prepared L-tryptophan amide, m. p. 167—170°, from the acid chloride hydrochloride and ammonia, but gave inadequate details. The present product was characterised as the *picrate* which separated from alcohol in excellent yield as orange-red needles and after recrystallisation from the same solvent had m. p. 241° (decomp.) (shrinking and becoming dark from 224°) (Found : C, 47·4; H, 4·0; N, 19·2. $C_{11}H_{13}ON_3,C_6H_3O_7N_3$ requires C, 47·2; H, 3·7; N, 19·4%).

4-3′-*Indolylmethyl*-2-*thio*-5-*thiazolidone* (II).—A solution of tryptophan amide (0·5 g.) in alcohol (10 ml.) was kept with concentrated aqueous ammonia (*d* 0·88; 0·5 ml.) and carbon disulphide (0·5 ml.) at room temperature for 2 hours. The solution was then heated to 40°, acidified with concentrated hydrochloric acid (2 ml.), and kept at 35—40° for 30 minutes. On

dilution with water (20 ml.) ammonium chloride redissolved and a very pale cream-coloured flocculent precipitate separated (0·27 g.). 4-3′-*Indolylmethyl*-2-*thio*-5-*thiazolidone* crystallised from acetone–water or chloroform–light petroleum as fine very pale cream-coloured needles, m. p. 188—191° (decomp., after shrinking at 180°) (heating from 160° at 5°/min.; slower heating resulted in indefinite decomposition above 220°) (Found: C, 55·0; H, 4·1; N, 10·7. $C_{12}H_{10}ON_2S_2$ requires C, 54·9; H, 3·8; N, 10·7%).

4-3′-Indolylmethyl-2-thio-5-thiazolidone (0·2 g.) was dissolved in a solution of sodium (0·05 g.) in methanol (5 ml.) and kept at room temperature for 2 hours. The yellow solution was acidified with methanolic hydrogen chloride, filtered from sodium chloride, and evaporated *in vacuo* to leave a yellow powder. Recrystallisation from methanol–ether gave tryptophan methyl ester hydrochloride (0·16 g.), m. p. 225° (decomp.) (softening 221°) not depressed by admixture with an authentic specimen.

4-3′-*Indolylmethylene*-2-*thio*-5-*thiazolidone* (IV).—(*a*) Indole-3-aldehyde (Elks, Elliot, and Hems, *loc. cit.*) (0·5 g.), 2-thio-5-thiazolidone (0·45 g.), and zinc chloride (0·5 g.) were refluxed in ethyl acetate (15 ml.) for 15 minutes. After cooling to 0° the solid was collected and washed with acetone and then with water. A small second crop obtained by concentration of the ethyl acetate filtrate brought the total yield of 4-3′-*indolylmethylene*-2-*thio*-5-*thiazolidone* to 0·48 g. (54%), the product crystallising from acetone–water in fine orange needles, m. p. 279° (decomp.).

(*b*) 4-Ethoxymethylene-2-thio-5-thiazolidone (18·9 g.) was dissolved in hot acetic acid (500 ml.). Indole (11·7 g.) was added and the resulting red solution refluxed for 6 hours, during which an orange-brown solid gradually separated. After cooling to room temperature the product (20·9 g., 80%) was collected. It was only very sparingly soluble in most solvents, and was purified by dissolution in a large volume of boiling acetone and dilution with water, separating as orange needles, m. p. 279° (decomp.), identical with the product from method (*a*) (Found: C, 55·5; H, 3·35; N, 10·6; S, 24·1. $C_{12}H_8ON_2S_2$ requires C, 55·4; H, 3·1; N, 10·8; S, 24·6%).

5-3′-*Indolyl*-2-*thiothiazolidine*-4-*carboxylic Acid* (V).—4-3′-Indolylmethylene-2-thio-5-thiazolidone (10 g.) was dissolved in a solution of potassium hydroxide (4·5 g.) in methanol (150 ml.) and kept at room temperature for 5 days, during which the colour gradually faded from very dark to light red. Evaporation *in vacuo* left a red gum which was dissolved in water (50 ml.) and acidified with concentrated hydrochloric acid (10 ml.), the product separating as a red-brown plastic mass. Partial purification was effected by dissolution in aqueous sodium hydrogen carbonate, acidification of the filtered solution yielding an orange gum which solidified in the refrigerator overnight to a buff powder (8·36 g.), m. p. 169—170° (decomp.). 5-3′-*Indolyl*-2-*thiothiazolidine*-4-*carboxylic acid* crystallised from acetone–chloroform in colourless needles, m. p. 187—188° (decomp.) (Found: C, 51·7; H, 3·7; N, 10·1; S, 23·3. $C_{12}H_{10}O_2N_2S_2$ requires C, 51·8; H, 3·6; N, 10·1; S, 23·0%).

5-3′-*Indolylmethylene*-2-*thiohydantoin* (VII).—4-3′-Indolylmethylene-2-thio-5-thiazolidone (10 g.) was dissolved in aqueous ammonia (*d* 0·88; 100 ml.) and the blood-red solution heated on the steam-bath for 3 hours, during which orange crystals separated. The mixture was diluted with water (100 ml.), cooled, and filtered, and the crude product (5·73 g.) washed with water. 5-3′-*Indolylmethylene*-2-*thiohydantoin* crystallised from acetic acid as orange needles, decomp. 310—315° (Found: C, 55·7; H, 4·35; N, 13·8; S, 10·5. $C_{12}H_9ON_3S,C_2H_4O_2$ requires C, 55·4; H, 4·3; N, 13·9; S, 10·6%).

5-3′-*Indolylmethylenehydantoin*.—A suspension of the crude thiohydantoin (2 g.) in acetic acid (300 ml.), chloroacetic acid (50 g.) and water (100 ml.) was refluxed for 5½ hours, a clear orange-red solution being obtained after 7 minutes' boiling. On cooling to room temperature a first crop of 5-3′-indolylmethylenehydantoin (1·44 g.) separated and concentration of the filtrate to about 100 ml. gave a further 0·27 g. Recrystallisation from acetic acid gave the hydantoin as a lemon-yellow powder, m. p. 334° (slight darkening from 331°) (Found: N, 18·6. Calc. for $C_{12}H_9O_2N_3$: N, 18·5%), identical with an authentic specimen of 5-3′-indolylmethylenehydantoin prepared by the condensation of indole-3-aldehyde and hydantoin in boiling piperidine (Shabica, Howe, Ziegler, and Tishler, *J. Amer. Chem. Soc.*, 1946, **68**, 1156).

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59. *The Solubility of the Copper Salts of Aromatic Carboxylic Acids in Benzene–Ethanol Mixtures.*

By Malcolm Crawford and F. H. C. Stewart.

The solubilities in benzene containing 10% of ethanol of the copper salts of a number of substituted benzoic acids have been determined. The presence of *ortho*-groups causes high solubility, *meta*-groups impart low solubility, and *para*-groups insolubility. The very few exceptions to these generalisations are considered. The effect of *ortho*-substituents is believed to be due to weakening of the crystal lattice resulting from enforced coplanarity of the carboxylate group with the aromatic ring. Such a strained lattice dissolves more readily in a solvent containing a solvating agent. The carboxylate group in the dissolved molecules will then be out of the plane of the ring. The other effects are also explained.

Certain copper carboxylates are more soluble in mixtures of ethanol and benzene than in either of the pure solvents; in the case of copper diphenylacetate this is due to the formation of an isolable complex of the salt with two molecules of ethanol (Crawford, *J.*, 1950, 2187), the complex being soluble in benzene whereas the salt is not. In the case of other copper salts, such as the phenylacetate, the complex cannot be isolated but its presence in solution is doubtless responsible for the solubility of the salt in the mixed solvents.

This work was extended by determining the solubility of other copper carboxylates in ethanol (1 vol.)–benzene (9 vol.) at 25°. Solubility in the fatty acid series increases rapidly from the insoluble formate (Crawford, *Nature*, 1950, **165**, 728) to the very soluble *n*-butyrate. The higher members are low-melting substances readily soluble in organic solvents. The solubility of the salts of unsaturated acids depends considerably on stereochemical configuration (Crawford, *Chem. and Ind.*, 1951, 234).

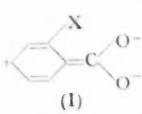
The copper salts of aromatic acids have now been examined in an attempt to explain the previous finding that the salts of many *ortho*-acids are soluble whereas the *para*-salts are insoluble in the standard solvent. It has also been noted that other physical properties vary, thus copper *o*-chlorobenzoate is bright green whereas the *para*-salt is light greenish-blue. This distinctive behaviour is of course paralleled by the known *ortho*-effects exhibited by the acids themselves. It is therefore of interest to discover whether the high solubility of the *ortho*-salts is due to the operation of an *ortho*-effect in the parent acid.

The solubilities of a number of *ortho*- and *para*-salts are presented in Table 1; values

Table 1. *Solubility of copper salts in the standard solvent* (g./100 g.) *at* 25°.

o-Fluorobenzoate	3·0	*p*-Fluorobenzoate	0	*o*-Bromobenzoate	5·7	*p*-Bromobenzoate	0
o-Chlorobenzoate	2·5	*p*-Chlorobenzoate...	0	*o*-Iodobenzoate ...	6·0	*p*-Iodobenzoate ...	0
o-Toluate	6·0	*p*-Toluate	0	Diphenyl-2-carboxylate	20	Diphenyl-4-carboxylate	0
α-Naphthoate ...	5·9	β-Naphthoate	0				

above 20 g. per 100 g. of solvent are of lower accuracy, because of experimental difficulties. The fact that a compound has high solubility is sufficient evidence for the arguments developed later. It was suggested (Crawford, *Nature, loc. cit.*), following Baddeley (*Nature*, 1939, **144**, 444), that the high solubility of *ortho*-salts, similarly to the effects shown by *ortho*-carboxylic acids generally, is due to the steric influence of the *ortho*-substituent, which would prevent the carboxyl group from lying in the plane of the benzene ring and therefore from entering into resonance with it. Consequently, forms such as (I) would be unable to contribute to the state of the molecule; hence, with the resultant decrease in ionic character, the intermolecular bonding forces in the crystal lattice would be diminished and attack by solvent and solvating molecules made easier. To establish the steric nature of the effect it is necessary to study the influence of the size of the *ortho*-substituent on solubility.



(I)

A halogen atom is unsuitable as the *ortho*-substituent, since electrical influences also vary, from one halogen to another. Alkyl substituents were therefore chosen, as their

size can be varied while their electrical effects can be kept at a minimum. The results of solubility determinations on the copper salts of such acids are given in Table 2. The

TABLE 2.

	Copper salt solubility		Copper salt solubility	M. p. of acid
o-Toluate	6·0	*p*-Toluate	0	175°
o-Ethylbenzoate	16·8	*p*-Ethylbenzoate	0·72	113
o-*iso*Propylbenzoate	23	*p*-*iso*Propylbenzoate	0·74	115
o-*tert*.-Butylbenzoate	35	*p*-*tert*.-Butylbenzoate	0	166

ortho-salts also differ in appearance from the *para*-compounds; they vary from a bright greenish-blue (*o*-toluate) to a brilliant deep blue (*o*-*tert*.-butylbenzoate) whilst the *para*-salts are pale blue.

The solubility differences leave little doubt that the size of the substituent is an important factor. Electrical effects are likely to be slight; hyperconjugation would operate in the same direction, rendering the *tert*.-butylbenzoate less ionic and therefore more soluble, whereas the inductive effect would oppose this. Even the strong inductive effect in *o*-halogenated salts is not sufficient to suppress solubility. Hence to account for the difference between *o*- and *p*-halogenated salts steric factors must be invoked.

A logical assumption would be that the carboxyl group is rotated more and more out of the plane of the ring, but it would perhaps be better to suppose that in the crystal lattice there is a certain strain energy associated with the carboxyl group due to compulsory coplanarity with the ring. The idea of a strained crystal lattice is not unreasonable since the strain energy resulting from enforced coplanarity would only be a fraction of the lattice energy gained in packing molecules into the crystal. A compound with a strained lattice would dissolve more readily than an unstrained one in a solvent containing a solvating agent. The larger or bulkier the *ortho*-substituent, the greater will be the strain energy and hence the higher the solubility.

It would then be expected that 2 : 6-disubstituted benzoic acids would form very soluble copper salts; this is confirmed by the following figures for the solubility of copper salts in the standard solvent (g./100 g.) at 25°: 2 : 6-dimethylbenzoate, 40; 2 : 4 : 6-trimethylbenzoate, 35; 4-*tert*.-butyl-2 : 6-dimethylbenzoate, 30; and 2-methyl-1-naphthoate, 35.

Another factor which might be involved in copper salt solubility is acid strength; it is clear that the two increase in step. However, in the fatty acid series acid strength decreases while copper salt solubility increases from formic to butyric acids. Examination

TABLE 3. *Acid strength and copper salt solubility.*

Acid	10^5K	Salt solubility	Acid	10^5K	Salt solubility
$C_6H_5{\cdot}CO_2H$	6·5	0·1	2 : 4 : 6-$Me_3C_6H_2{\cdot}CO_2H$	37·0 *	35
o-Me·$C_6H_4{\cdot}CO_2H$	13·5	6·0	2 : 6-$Me_2C_6H_3{\cdot}CO_2H$	62·0	40
o-Bu^t·$C_6H_4{\cdot}CO_2H$	35·1	35			

* The dissociation constant is given in Beilstein, **9**, 553 as $3{\cdot}75 \times 10^{-5}$ and in "International Critical Tables," Vol. VI, p. 295, as $3{\cdot}7 \times 10^{-4}$; the same unavailable references are cited. It is assumed by analogy with 2 : 6-dimethylbenzoic acid that the value given in Beilstein is a misprint.

of other series does not reveal any significant interconnection. Acid strength and copper salt solubility are most probably being influenced similarly by the presence of the bulky *ortho*-group. Indeed it has been shown (cf. Burkin, *Quart. Reviews*, 1951, **5**, 16) that the more basic a ligand, the more stable are the metal complexes formed by it.

The stability of the complexes of copper salts with alcohols is low and is probably a much less important factor in determining solubility than the lattice stability of the uncomplexed salts. The solubility apparently depends largely on the ease of disintegration of the crystal lattice by the benzene–ethanol rather than on any marked stability of the complexes formed in solution. The effect of substituents known to have a weakening influence on lattice stability was therefore examined. Since the melting point of an organic compound is mainly a measure of the ease of disintegration of the crystal lattice,

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it follows that any substituent which has a marked lowering effect on the melting-point should be suitable for this purpose. Ethyl, propyl, and *iso*propyl groups are known to exert such an effect, generally in much greater measure than methyl or *tert.*-butyl groups. The solubilities of the copper salts of various low-melting *m*-alkylbenzoic acids and those of the higher-melting methyl and *tert.*-butyl analogues have therefore been determined:

m-Substituent	Me	Et	Pr^n	Pr^i	Bu^t
M. p. of acid	110°	45°	43°	47°	127°
Solubility of copper salt	1·9	3·1	3·0	3·0	4·8

Compared with results given in Table 2 for salts of *para*-substituted acids, these results show that the presence of an ethyl group, for example, has a small, though real effect on copper-salt solubility. It would also appear from these two Tables that groups such as ethyl, propyl, and *iso*propyl, which have a profound effect in lowering the melting-point of an acid, also have the power to impart slight solubility to its copper salt, which would otherwise be insoluble.

The presence, in the *meta*-position, of a substituent not having a marked lowering influence on melting point, *e.g.*, methyl or *tert.*-butyl, nevertheless causes the copper salt to be appreciably soluble. This is confirmed by the solubilities of a range of copper *meta*-substituted benzoates in the standard solvent (g./100 g.) at 25°: *m*-fluorobenzoate, 1·5; *m*-chlorobenzoate, 1·5; *m*-bromobenzoate, 1·09; *m*-iodobenzoate, 1·04; 3-bromo-4-methylbenzoate, 0·8; diphenyl-3-carboxylate, 0·87; 3:4-dimethylbenzoate, 1·3. These salts are seen to be appreciably soluble in benzene–ethanol, which would not be expected if solubility depended entirely on a steric *ortho*-effect.

The solubility of the copper *meta*-substituted benzoates can be taken as evidence in support of ease of lattice disintegration as a factor in copper-salt solubility. The introduction of almost any group into the *meta*-position will result in the production of a more open crystal lattice, which of course will not only be more exposed to solvent attack but will possess a lower lattice energy. This conception is supported by the considerable effect of the bulky *tert.*-butyl group in increasing solubility. Lattice widening will also occur in the *ortho*-substituted benzoates but is masked by the much greater steric effect of the *ortho*-group.

The solubility of copper salts of aromatic carboxylic acids in benzene–ethanol depends therefore upon a number of factors of varying intensity: (1) the presence of groups known to lower the melting point, a slight effect, (2) the presence of *meta*-substituents, also a small effect probably due to lattice widening in the crystal, and (3) the presence of an *ortho*-substituent, which is the major and most firmly established factor, which operates by steric action on the carboxyl group.

Experimental

Preparation of Copper Salts.—(a) *Precipitation method.* The pure acid was neutralised (to phenolphthalein) with dilute sodium hydroxide solution. A slight excess of aqueous analytical grade copper sulphate was added with stirring, and the mixture boiled. The washed and dried copper salt was crystallised from benzene–ethanol whenever possible.

(b) *Copper carbonate method.* This method was used whenever the copper salt was soluble in water. The pure acid and an excess of copper carbonate were boiled in a large volume of water, the excess of carbonate was filtered off and the filtrate was evaporated to dryness, and the residual copper salt purified as already described.

Copper was determined by the salicylaldoxime method.

Solubility Determinations.—The dried copper salt was shaken in a stoppered vessel with benzene–ethanol (9:1, by volume) for 2—3 days at 25°. The saturated solution was quickly filtered into a tared weighing bottle, which was then stoppered and weighed. The solvent was evaporated and the residue dried to constant weight at 110°. The solubility is expressed in g. of salt per 100 g. of solvent, not as in previous papers. With values above 20 it was difficult to obtain reproducible results and such values are given to the nearest whole number.

Copper Salts.—The following copper salts were used [prepared by method (*a*), unless otherwise stated; solubility refers to *hot* benzene–ethanol, from which solvent the salts were crystallised unless otherwise specified].

Benzoate, a slightly soluble, blue powder (Found: Cu, 20·7. Calc. for $C_{14}H_{10}O_4Cu$: Cu, 20·8%). o-*Toluate*, very soluble, blue needles (Found: Cu, 18·9. $C_{16}H_{14}O_4Cu$ requires Cu, 19·0%). m-*Toluate*, small bluish-green, solvated crystals (solvent lost on exposure, giving a blue powder) (Found: Cu, 18·9%). *p*-Toluate, an insoluble blue powder (Found: Cu, 19·3%) (previously prepared by Noad, *Annalen*, 1848, **63**, 294).

Diphenyl-2-carboxylate, very soluble, deep blue solvated octahedra (the bluish-green salt obtained by removal of the solvent at 100° was thermochromic) (Found: Cu, 13·7. Calc. for $C_{26}H_{18}O_4Cu$: Cu, 13·9%) (previously prepared by Weger and Döring, *Ber.*, 1903, **36**, 881). *Diphenyl-3-carboxylate* (the acid was prepared by oxidation of 3-methyldiphenyl, obtained by Gomberg reaction on *m*-toluidine), soluble, blue needles (Found: Cu, 13·7%). *Diphenyl-4-carboxylate* (the acid was prepared as for the 3-isomer), an insoluble, pale blue powder (Found: Cu, 14·1%). α-*Naphthoate*, soluble, green needles (Found: Cu, 15·7%. $C_{22}H_{14}O_4Cu$ requires Cu, 15·7%). β-*Naphthoate*, an insoluble, pale blue powder (Found: Cu, 15·9%). 2-*Methyl*-1-*naphthoate*, bright green, solvated needles, from ethanol (solvent lost at 100°, with colour change) (Found: Cu, 14·5. $C_{24}H_{18}O_4Cu$ requires Cu, 14·6%).

o-Ethylbenzoate, a very soluble, bluish-green powder (Found: Cu, 17·3. Calc. for $C_{18}H_{18}O_4Cu$: Cu, 17·6%) (Giebe, *Ber.*, 1896, **29**, 2534, prepared this compound). m-*Ethylbenzoate*, soluble bluish green needles (Found: Cu, 17·4%). *p*-Ethylbenzoate, somewhat soluble, pale blue, thermochromic needles (Found: Cu, 17·3%) (previously prepared by Fittig and König, *Annalen*, 1867, **144**, 292).

The o-iso*propylbenzoate* was very soluble in ethanol from which it separated in green plates, which lost ethanol when heated, giving a dark blue salt (Found: Cu, 16·2. $C_{20}H_{22}O_4Cu$ requires Cu, 16·3%). m-iso*Propylbenzoate*, very soluble, greenish-blue needles (Found: C, 16·1%). p-iso*Propylbenzoate*, soluble, thermochromic blue needles (Found: C, 15·9%); the parent acid was prepared as follows: The Grignard reagent from the mixed isomers obtained by bromination of cumene was treated with carbon dioxide, the copper salts of the resulting mixed acids were separated by extraction with benzene–ethanol, and the less soluble *para*-salt was purified through the parent acid (m. p. 115°; from hot water). m-*Propylbenzoate*, small blue needles (Found: C, 16·1%).

o-tert.-*Butylbenzoate* was very soluble in ethanol but crystallised from methanol in dark green leaflets, which crumbled at 100° to a deep blue powder (Found: Cu, 15·3. $C_{22}H_{26}O_4Cu$ requires Cu, 15·2%). m-tert.-*Butylbenzoate*: method (a) gave the salt as a greenish-blue powder, soluble in hot benzene–ethanol; evaporation of this solution gave a duck-egg blue powder, insoluble in this solvent; the original powder became purple, then pale green when heated, and its solution in benzene–ethanol gave soluble green crystals [Found: Cu, 14·8 (duck-egg blue powder); Cu, 14·9% (recrystallised pale green powder)]. p-tert.-*Butylbenzoate*, an insoluble, pale blue (deepening when heated) powder (Found: C, 15·3%); the acid was prepared by Verley's method (*Bull. Soc. chim.*, 1898, **19**, 72).

2 : 6-*Dimethylbenzoate*, obtained as a green salt in poor yield by method (*a*) and in better yield by method (b) as a brown product, formed solvated, dark green octahedra from ethanol, or solvent-free needles (sometimes green, sometimes reddish-brown, and sometimes a mixture) from benzene–ethanol (Found: Cu, 17·4. $C_{18}H_{18}O_4Cu$ requires Cu, 17·6%); the parent acid, m. p. 116°, was prepared from 2 : 6-dimethylaniline through 2-bromo-*m*-xylene by Sandmeyer and Grignard reactions. 2 : 4 : 6-*Trimethylbenzoate*, preferably prepared by method (b), formed green solvated crystals from ethanol or acetone; the solvent-free salt was a green powder (Found: Cu, 16·1. $C_{22}H_{26}O_4Cu$ requires Cu, 16·3%). 4-tert.-*Butyl*-2 : 6-*dimethylbenzoate*, green solvated leaflets, from ethanol containing a little benzene; when heated these gave a dark blue powder (Found: Cu, 13·3. $C_{26}H_{34}O_4Cu$ requires Cu, 13·4%). 3-*Bromo*-4-*methylbenzoate*, a soluble blue powder (Found: Cu, 12·9. $C_{16}H_{12}O_4Br_2Cu$ requires Cu, 12·9%); the acid, m. p. 202°, was readily obtained by bromination of *p*-toluic acid by Derbyshire and Waters's method.

o-*Fluorobenzoate*: method (b) gave a pale blue, partially soluble, powder; the residue was Slothouwer's basic salt (*Rec. Trav. chim.*, 1914, **33**, 325); the solution gave the greenish-blue normal salt (Found: Cu, 18·2. $C_{14}H_8O_4F_2Cu$ requires Cu, 18·6%). *m*-Fluorobenzoate always contained some basic salt (Found: Cu, 23·0%). *p*-Fluorobenzoate also always contained some basic salt (Found: Cu, 24·1%).

o-*Chlorobenzoate*, green needles by method (b) (Found: Cu, 16·7. $C_{14}H_8O_4Cl_2Cu$ requires Cu, 17·0%). m-*Chlorobenzoate*, blue crystals (Found: Cu, 16·9%). p-*Chlorobenzoate*, an insoluble pale blue powder (Found: Cu, 17·2%), distinct from the dihydrate reported by Ephraim and Pfister (*Helv. Chem. Acta*, 1925, **8**, 379).

o-*Bromobenzoate*, preferably prepared by method (b), formed green needles (Found: Cu, 13·5. $C_{14}H_8O_4Br_2Cu$ requires Cu, 13·7%); Rhalis (*Annalen*, 1879, **198**, 107) has described a monohydrate. m-*Bromobenzoate*, green needles which lose solvent readily to give a very deep blue powder (Found: Cu, 13·8%). p-*Bromobenzoate*, an insoluble pale blue powder (Found: Cu, 13·7%).

o-*Iodobenzoate*, yellowish needles from benzene or green solvated needles from benzene–ethanol (Found: Cu, 10·5. $C_{14}H_8O_4I_2Cu,C_2H_6O$ requires Cu, 10·5. Found, in material dried at 100°: Cu, 11·4. $C_{14}H_8O_4I_2Cu$ requires Cu, 11·4%). m-*Iodobenzoate*, blue crystals which crumble to a deep blue powder when heated (Found: Cu, 11·2%). p-*Iodobenzoate*, an insoluble, pale blue powder (Found: Cu, 11·3%).

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College of Technology, Belfast. [*Received, July 26th*, 1952.]

60. *The Isomeric Dithia*cyclo*pentenethiones.*

By Frederick Challenger, Ernest A. Mason, and (in part) Ernest C. Holdsworth and Robert Emmott.

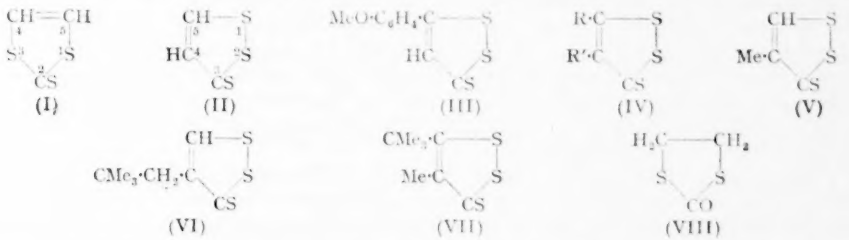
The reaction between acetylene and boiling sulphur gives, in addition to carbon disulphide, hydrogen sulphide, thiophen, dithienyls, thionaphthen, and the isomeric thiophthens, two isomeric compounds, identified as 1 : 3-dithia*cyclo*pent-4-ene-2-thione (I) and 1 : 2-dithia*cyclo*pent-4-ene-3-thione (II). The properties and reactions of these two compounds and their ultra-violet and infra-red spectra have been examined.

The reaction between acetylene and sulphur at about 450° yields large quantities of hydrogen sulphide, carbon disulphide, and thiophen together with a red oil, obtained by distillation in superheated steam. Fractionation of this oil gave (1) the isomeric thiophthens, b. p. 90—120°/15 mm. (Challenger and Harrison, *J. Inst. Pet. Tech.*, 1935, **21**, 135; Challenger, Clapham, and Emmott, *J. Inst. Pet.*, 1948, **34**, 922; Challenger and Emmott, *ibid.*, 1951, **37**, 395), (2) the isomeric dithienyls, b. p. 120—140°/15 mm. (Bruce, Challenger, Gibson, and Allenby, *ibid.*, 1948, **34**, 226), and (3) a dark red oil, b. p. 140—165°/15 mm. The yield of this oil was greater at lower reaction temperatures, and the yield of the isomeric thiophthens decreased accordingly, suggesting that some interconversion occurs.

Fraction (3) deposited a bright orange solid with an unpleasant odour. Fractional crystallisation gave some deep-orange prisms and yellow needles, both of molecular formula $C_3H_2S_3$. The needles were at first incorrectly believed to be homogeneous and for brevity will be termed M.O.S. (mixed orange solids). They did not contain a thiol group, react with mercuric oxide or cyanide or with lead acetate, or form a picrate or give a colour with sulphuric acid or the indophenin reaction. Aniline gave hydrogen sulphide, indicating the presence of a thio-ketonic group. Addition products were formed with 1 mol. of methyl iodide, silver nitrate, cupric chloride, silver and copper azides, mercuric chloride, and cyanogen bromide. With chlorine, bromine, and iodine, dihalides were formed by addition; water regenerated M.O.S. Treatment of the mercurichloride with potassium iodide also regenerated M.O.S. but the product, although still having the composition $C_3H_2S_3$, was much paler and slightly lower-melting. A similar difference was noticed on regenerating M.O.S. from the silver azide compound. The behaviour towards cyanogen bromide suggested that M.O.S. might contain two ingredients of different reactivity. Further crystallisation of M.O.S. was ineffective but a complete separation in benzene was obtained by chromatography on active alumina, yielding a yellow and an orange solid. Analysis and determination of molecular weight in each case agreed with the formula $C_3H_2S_3$. Structures (I) and (II) are proposed for these yellow and orange solids respectively. Pure (I) was also obtained by boiling M.O.S. with aqueous sodium hydroxide, (II) being destroyed.

Reactions of 1 : 2-*Dithia*cyclo*pent-4-ene-3-thione* (II), m. p. 82°.—A compound of this structure incorrectly termed "propylene trithione," had been prepared from propylene and sulphur (Lüttringhaus, König, and Böttcher, *Annalen*, 1948, **560**, 201). The structure was

determined from its mode of formation and the reactions of the analogous "*p*-anisyltrithione," (III), prepared from ethyl *p*-methoxycinnamate, sulphur, and phosphorus pentasulphide at 250°. Oxidation and degradation reactions were studied. Many other substituted "trithiones" of the type (IV) were obtained from α-methylstilbene and other



substituted ethylenic hydrocarbons and sulphur, and their reactions studied (Böttcher and Lüttringhaus, *Annalen*, 1947, **557**, 89; Böttcher, *Ber.*, 1948, **81**, 376; Böttcher and Bauer, *Annalen*, 1950, **568**, 218; *Ber.*, 1951, **84**, 289; Lüttringhaus and Cleve, *Annalen*, 1951, **575**, 112).

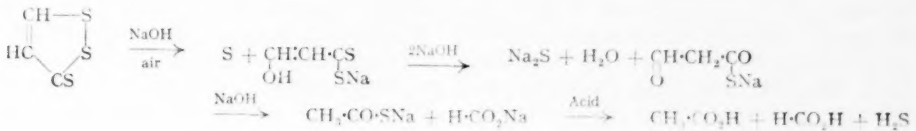
(*a*) Sulphur and *iso*butylene and (*b*) sulphur and di*iso*butylene below 200° were shown by Spindt, Stevens, and Baldwin (*J. Amer. Chem. Soc.*, 1951, **73**, 3693) to give a compound of structure (V) from (*a*), and two isomeric compounds (VI) and (VII) from (*b*). Several similar compounds have been prepared by Voronkov, Broun, and Karpenko (*J. Gen. Chem., Russia*, 1949, **19**, 1927; *Chem. Abs.*, 1950, **44**, 1955) from sulphur and olefins of the type R·CH:CRMe or R·CH_2·CR:CH_2. They gave addition products with metallic salts and methyl iodide. Schmitt and Lespagnol (*Compt. rend.*, 1950, **230**, 551) describe a number of compounds analogous to (II), prepared from sulphur and arylpropylenes.

"Propylene trithione," prepared by Lüttringhaus, König, and Böttcher's method (*loc. cit.*), had m. p. 82°, was similar in appearance to (II), and gave no depression in m. p. on mixing. The methiodide and mercurichloride of the two products were also identical. The formation of (II) in our work may be due to acetone with which the acetylene (from a cylinder) was contaminated. Under the experimental conditions this might yield propylene. The reaction has not been carried out in absence of acetone.

The ultra-violet spectrum of (II) (see p. 296) closely resembles those obtained for the "trithiones" by Lüttringhaus and Cleve (*loc. cit.*) and by Spindt, Stevens, and Baldwin (*loc. cit.*). Its infra-red spectrum (p. 297) also agrees with the structure assigned. Bromine in carbon tetrachloride gives a dibromide which is unstable to water, regenerating (II) (see p. 292). This suggests that the double bond is not involved. The disulphide link appears to be unreactive. Potassium cyanide gives no thiol, and with mercuric chloride the resulting addition product readily regenerates (II), suggesting that the >C:S and not the ·S·S· group is involved. Aliphatic disulphides R·S·S·R undergo fission with mercuric chloride, giving R·S·HgCl and other products (Challenger and Rawlings, *J.*, 1937, 868).

No oxime was obtained with hydroxylamine, although 4-*p*-methoxyphenyl-1 : 2-dithia*cyclo*pent-4-ene-3-thione gives one (Böttcher and Lüttringhaus, *loc. cit.*). With sodium and alcohol, (II) gave hydrogen sulphide and traces of a thiol. However, butenethiols, sodium, and methyl alcohol in liquid ammonia give *n*-butenes (Birch and McAllan, *J.*, 1951, 2556), and possibly propylene may have been formed from (II).

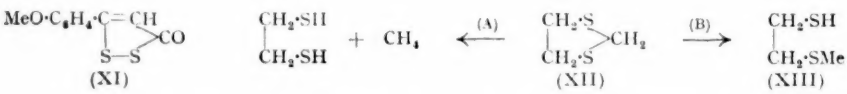
With hot aqueous sodium hydroxide, (II) gave hydrogen sulphide, free sulphur, and a formate. The following mechanism for this reaction is proposed, by analogy with a similar reaction (Böttcher and Lüttringhaus, *loc. cit.*) on 4-*p*-methoxyphenyl-1 : 2-dithia*cyclo*pent-4-ene-3-thione :



Triphenylphosphine gave triphenylphosphine sulphide. Schönberg and Krüll (*Ber.*, 1926, **59**, 1403) obtained triethylphosphine sulphide from di-*p*-methoxyphenyl thioketone and triethylphosphine. Grote's reagent (*J. Biol. Chem.*, 1931, **93**, 25) gave a positive test for the dithio-acid group, ·S·CS·.

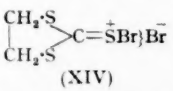
Reactions of 1 : 3-*Dithia*cyclo*pent*-4-*ene*-2-*thione* (I), *m. p.* 50°, *b. p.* 122—123°/0·8 *mm.*—The compound (I) gave a mono- and a di-mercurichloride which were decomposed by potassium iodide, regenerating (I); Bost and Cosby (*J. Amer. Chem. Soc.*, 1935, **57**, 1404) showed that thioketones form mercurichlorides. The monomethiodide regenerated (I) on decomposition with pyridine. Methyl sulphate in acetone yielded a solid which gave the monomethiodide with potassium iodide. Grote's reagent (*loc. cit.*) gave a positive test for the dithio-acid group with (I).

Comparison of Certain Reactions of Ethylene Trithiocarbonate and (I).—(*a*) *Ethylene trithiocarbonate.* The reaction of piperidine with ethylene trithiocarbonate (Husemann, *Annalen*, 1862, **123**, 67), together with that of other secondary amines (Delaby, Piganiol, and Warolin, *Compt. rend.*, 1950, **230**, 1671), was found to give compounds of the structure $R_2N{\cdot}CS{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}SH$. With piperidine and ethylene trithiocarbonate at room temperature we obtained the compound described by Delaby *et al.*, m. p. 108°. This, heated with excess of piperidine at 100°, was unchanged. Piperidine and ethylene trithiocarbonate at 100°, however, gave piperidinium piperidine-1-dithiocarboxylate, $C_5H_{10}N{\cdot}CS{\cdot}SH,C_5H_{10}NH$, and an unidentified white compound, $C_{16}H_{28}N_2S_4$, m. p. 212°, which was shown not to be a piperidinium salt. Reaction with propylene trithiocarbonate (Husemann, *Annalen*, 1863, **126**, 295) gave only the above piperidinium salt. Ethylene trithiocarbonate with dilute nitric acid at room temperature gives ethylene dithiocarbonate (VIII; see p. 293) (Husemann, *ibid.*, p. 269), which was obtained by us from ethylene trithiocarbonate and mercuric acetate in acetic acid. It was hoped that dehydrogenation of the trithiocarbonate would occur to form (I), since mercuric acetate dehydrogenates emetine (Battersby and Openshaw, *J.*, 1949, S 67) and δ-lupanine (Manion and Leonard, *Canad. J. Chem.*, 1951, **5**, 360). However, Böttcher (*loc. cit.*) obtained the ketone (XI) from *p*-methoxyphenyl trithione and mercuric acetate. In our reaction, a white insoluble solid was also obtained, which with potassium hydroxide became orange and finally black. Hydrogen sulphide gave mercuric sulphide. Comparison with a specimen of $HgS,Hg(OAc)_2$ (Bernardi and Rossi, *Gazzetta*, 1922, **52**, i, 139) showed that the two compounds were probably identical. The black compound formed with alkali was probably HgS,HgO, since the white compound $2HgSe,HgCl_2$ also gives black 2HgSe,HgO on similar treatment (Uelsmann, *Annalen*, 1860, **116**, 126).

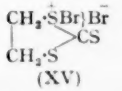


Reduction of ethylene trithiocarbonate and of diethyl trithiocarbonate with sodium and alcohol gave ethane-1 : 2-dithiol and ethanethiol, respectively (cf. Salamon, *J. pr. Chem.*, 1873, **6**, 446). In both cases hydrogen sulphide but no methanethiol was evolved on acidification. It seemed possible that, in the case of ethylene trithiocarbonate, 1 : 3-dithiolan (XII) might be an intermediate product yielding ethane-1 : 2-dithiol and methane on further reduction according to (A). However, this is not the case, since we find that reduction of 1 : 3-dithiolan (Gibson, *J.*, 1930, 13) gave 2-methylthioethanethiol (XIII) in good yield according to (B). This was characterised by comparison with a synthetic specimen prepared from sodium methyl sulphide and ethylene sulphide (Meade and Woodward, *J.*, 1948, 1894). The isomeric thiol $CH_3{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}SH$ (Böhme, Fischer, and Frank, *Annalen*, 1949, **563**, 67) was not detected. In all cases the thiols were identified as derivatives with mercuric cyanide or *p*-chloronitrobenzene or chloro-2 : 4-dinitrobenzene (Bost, Turner, and Norton, *J. Amer. Chem. Soc.*, 1932, **54**, 1985). We found that with sulphur at 200—230° 1 : 3-dithiolan gave ethylene trithiocarbonate and hydrogen sulphide. Wallach (*Annalen*, 1890, **259**, 302) obtained a thioketone from *pp'*-bisdimethylaminodiphenylmethane and sulphur. Ethylene trithiocarbonate formed a dibromide which evolved hydrogen bromide

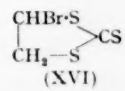
in moist air, and with cold water regenerated the trithiocarbonate. It probably has the structure (XIV) or less probably (XV).



(XIV)



(XV)



(XVI)

A compound such as 1 : 4-dithian gives a tetrabromide and this on hydrolysis gives the corresponding disulphoxide (Husemann, *Annalen*, 1863, **126**, 287). The thermal decomposition of the dibromide (XIV or XV) was then studied. It was hoped that elimination of two molecules of hydrogen bromide and formation of (I) might occur or else that hydrogen bromide and a monobromo-derivative (XVI) might be formed. Further elimination of halogen acid with pyridine might then yield (I). However, the decomposition was complex; ethylene dibromide, sulphur bromide, hydrogen bromide, and traces of sulphur and carbon disulphide were formed.

(*b*) *Reactions of* (I). Piperidine at 100° gave piperidinium piperidine-1-dithiocarboxylate (see p. 296), affording clear evidence for the grouping –S–C(:S)– or –S–C(=S)–S– (A).* When boiled with neutral hydroxylamine, (I) gave hydrogen sulphide, sulphur, glyoxime, and thiosulphate, probably by the reactions :

The last stage is analogous to the formation of glyoxal phenylosazone from phenylhydrazine and glycollaldehyde (Fisher and Landsteiner, *Ber.*, 1892, **25**, 2553). The formation of glyoxime establishes the presence of two adjacent carbon atoms (B). The non-formation of (I) from propylene and sulphur is evidence against the presence of three adjacent carbon atoms therein.

Evidence of the presence of a monothione group in (I) was obtained by the action of mercuric acetate (C) which gave the compound (XVII), together with an insoluble white solid (see p. 300). This ketone was unreactive to bromine and mercuric chloride, indicating that the addition compounds of (I) with these reagents involve the thioketonic and not the sulphide group. The normal ketone reactions with hydroxylamine, semicarbazide, or 2 : 4-dinitrophenylhydrazine failed. Attempts to establish the structure of (I) by catalytic hydrogenation of the ketone (XVII) to (VIII) were unsuccessful.

Aqueous-alcoholic sodium hydroxide with (I) gave a good yield of sodium trithiocarbonate, thus proving the presence of the trithiocarbonate group ·S·CS·S· (D). Alcoholic potassium hydroxide, however, gave traces of a thiol.

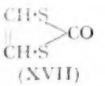
Strong evidence for the structure assigned to (I) was obtained by reduction with sodium and alcohol (E). Ethane-1 : 2-dithiol (Meyer, *Ber.*, 1886, **19**, 3263), identified as ethane bis-(2 : 4-dinitrophenyl sulphide) (see p. 299), and methanethiol, isolated as its mercury derivative, were obtained.

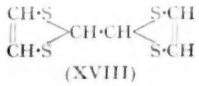
The formation of methanethiol recalls the reduction of phenyl *iso*thiocyanate with aluminium amalgam (Gutbier, *Ber.*, 1901, **34**, 2034). However, the reaction is complex, since much hydrogen sulphide is obtained together with traces of sulphides and other products. Probably the intermediate product is ethylenedithiol which could then lose hydrogen sulphide giving polymeric products. Hydrolysis by sodium ethoxide (see above) may also occur, accounting for the low yield of methanethiol. The production of ethane-1 : 2-dithiol in the reduction indicates the presence of the linkage ·S·C·C·S· in the molecule, and that of methanethiol the linkage ·C·S· (E). Reduction of (I) with lithium aluminium hydride in dry ether was a much smoother reaction than that with sodium and alcohol, the product again being ethane-1 : 2-dithiol.

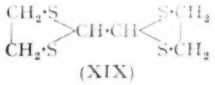
Potassium hydrogen sulphide in absolute alcohol caused fission of (I), giving potassium trithiocarbonate in good yield and a thiol, which yielded a 2 : 4-dinitrophenyl sulphide

* Letters so used refer to structures or reactions regarded as establishing the constitution of (I) (see p. 296).

in the usual way (F). Analysis of this derivative indicated that it was possibly $(NO_2)_2C_6H_3{\cdot}S{\cdot}CH{:}CH{\cdot}S{\cdot}C_6H_3(NO_2)_2$. Its melting point was different from that of the corresponding ethane derivative. It did not, however, combine with bromine in chloroform and its structure is uncertain. In view of the importance of reaction (F) for the structure of (I), further work is in progress.


(XVII)


(XVIII)


(XIX)

Reduction of (I) with zinc and acetic acid gave hydrogen sulphide and a substance $(C_3H_3S_2)_2$ which may be (XVIII). An attempt to obtain this by dehydrogenation of glyoxal bisethylenemercaptal (XIX) (Fasbender, *Ber.*, 1888, **21**, 1476) with sulphur was unsuccessful.

The compound (I) gave a dibromide which evolved hydrogen bromide in moist air and was hydrolysed by cold water, regenerating (I). Thermal decomposition gave hydrogen bromide and an insoluble black solid, which could not be purified. No sulphur bromide was detected. This result was disappointing as it was hoped that dibromoethylene would be isolated, thus confirming the presence of a $\cdot CH{:}CH\cdot$ linkage in (I) (compare p. 295). The reactions A–F may, however, be regarded as establishing the structure assigned to (I). Further evidence for this is afforded by the spectroscopic data below. Triphenylphosphine had no action on (I) or on ethylene trithiocarbonate (see p. 295).

The catalytic reduction of (I) by various forms of platinum, palladium, or nickel was unsuccessful. With Raney nickel only nickel sulphide could be detected. Eight atoms of hydrogen were absorbed per molecule. Snyder and Cannon (*J. Amer. Chem. Soc.*, 1944, **66**, 155) showed that *S*-ethers of ethane-1 : 2-dithiol underwent two cleavages, one of which involved C–C fission: $2RH + 2CH_4 + 2H_2S \xleftarrow{Ni} R{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}SR \xrightarrow{Ni} 2RH +$ $CH_3{\cdot}CH_3 + 2H_2S$ (R = H or Ph). In these cases the products were hydrocarbons, and presumably (I) would give ethane and methane which could be easily lost. All attempts to synthesise (I) failed (see p. 303).

Ultra-violet spectroscopic analysis.

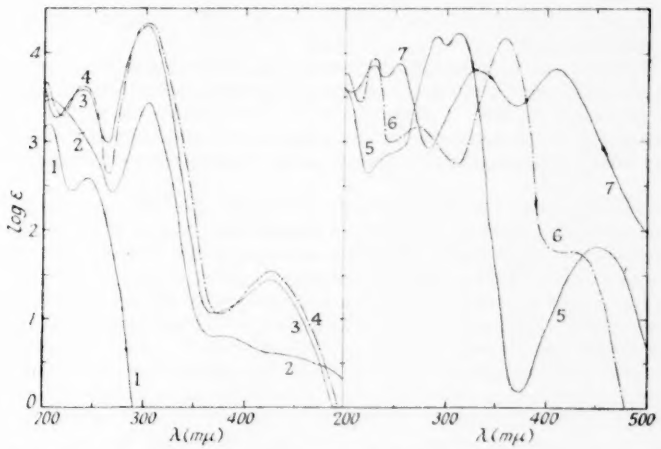
(Carried out with a "Unicam Quartz Spectrophotometer, S.P. 500," with *cyclo*hexane as solvent.)

Compound	$\lambda_{max.}$, mμ	ε	Compound	$\lambda_{max.}$, mμ	ε
1 : 3-Dithiolan	207	1,358	Ethylene trithiocarbonate	293	12,640
	247	367		311·5	14,780
				458	72·4
Methyl dithiopropionate ...	205	2,850			
	304·5	2,500	(I)	228·5	8,700
				276	1,440
Dimethyl trithiocarbonate	237·5	3,780		362	14,700
	302	16,900			
	430	28·0	(II)	230	7,450
				254	8,250
Diethyl trithiocarbonate ...	238	4,010		336	6,420
	305·5	19,400		415	6,700
	432	35·3			

The ultra-violet spectra of (I), ethylene trithiocarbonate, dimethyl trithiocarbonate (Cahours, *Ann. Chim.*, 1847, **19**, 162), diethyl trithiocarbonate (Husemann, *Annalen*, 1862, **123**, 67), methyl dithiopropionate (Houben and Schultze, *Ber.*, 1910, **43**, 2483), and 1 : 3-dithiolan (Gibson, *J.*, 1930, 13) indicated that (I) contained the trithiocarbonate group, which was probably conjugated since the principal maximum was shifted towards the long-wave region (Braude, *Ann. Reports*, 1945, **42**, 105). The trithiocarbonate group was shown to be a powerful chromophore by Purvis, Jones, and Tasker (*J.*, 1910, **97**, 2287). Our results show that the trithiocarbonate group gives a characteristic maximum, much higher than that for the dithiocarbonate group, and this is borne out by the results obtained by Purvis *et al.* (*loc. cit.*).

The structures (I) and (II) were further confirmed by measurements of the infra-red spectra in carbon tetrachloride solution. Professor Mecke writes "Eine vollständige Deutung der Spektren konnte von mir aus Zeitmangel noch nicht durchgeführt werden, jedoch gelang es in allen Fällen, die CS-Schwingung zu lokalisieren. Bei den ungesättigten Verbindungen [(I) und (II)] vermisse ich die Frequenz der Doppelbindung bei 1600, die

Absorption spectra in cyclohexane.



1, 1 : 3-*Dithiolan*. 2, *Methyl dithiopropionate*. 3, *Dimethyl trithiocarbonate*. 4, *Diethyl trithiocarbonate*. 5, *Ethylene trithiocarbonate*. 6, (I). 7, (II).

jedenfalls stark erniedrigt wurde. Somit besitzt der Ring stark aromatischen Charakter. Dass Verbindung (I) die höhere Symmetrie besitzt wie Verbindung (II) geht eindeutig daraus hervor, dass das Spektrum wesentlich einfacher gebaut ist, fast zu einfach."

An *X*-ray examination of (I), (II), and ethylene trithiocarbonate is being carried out by Professor E. G. Cox and Mr. V. Balashov in the University of Leeds. The substance (I) is monoclinic and its crystal structure is quite different from that of (II), which is tetragonal, and of the trithiocarbonate which is also monoclinic. *

Experimental

Preparation of the Mixed Orange Solids (M.O.S.).—The products of the reaction between acetylene, obtained from a cylinder and therefore containing acetone, and boiling sulphur at about 450°, after removal of carbon disulphide and thiophen at 100°, were distilled in superheated steam and fractionated. The mixed thiophthens contained in the fraction of b. p. 90—120°/15 mm. were removed. The fraction, b. p. 140—165°/15 mm., was repeatedly cooled in ice, giving a solid, which crystallised from alcohol in orange plates, m. p. 45—47° (Found: C, 26·9, 27·15; H, 1·65, 1·35; S, 70·4, 71·2%; *M*, cryoscopic in benzene, 142, 137·5, 139. Calc. for $C_3H_2S_3$: C, 26·9; H, 1·5; S, 71·6%; *M*, 134. Calc. for $C_3H_4S_3$: C, 26·5; H, 2·95; S, 70·6%; M, 136).

Typical yields. 27 and 20 Kg. of sulphur gave 25·5 and 39·0 g. of M.O.S., respectively. Introduction of extra acetone vapour into the acetylene gave increased yields of M.O.S., but increased yields were also obtained at about 400° and possibly the effect of the acetone was only to lower the reaction temperature: the yield of the isomeric thiophthens was lowered in each case.

Fractional crystallisation of M.O.S. The orange solid (m. p. 44—46°; 6·7 g.), which was mainly derived from the sulphur–acetylene–acetone process, was recrystallised nine times from light petroleum (b. p. 40—60°), but a constant m. p. could not be obtained although the long, hair-like, orange needles appeared homogeneous. Typical intermediate fractions had m. p.s 45—46° (giving a yellow mercurichloride, m. p. 195—197°), 44·5—45·5°, 43·5—45°, and 43·5—

* Further *X*-ray examination has confirmed the structure (I) for the orange solid, m. p. 50°.

46°. On the tenth crystallisation small orange crystals were deposited on the sides of the flask before the long orange needles. The needles were removed with the mother-liquor. The small orange crystals melted at 60—70°, at 78—81° after one crystallisation, and finally at 80—81·5° (constant). They appeared as glittering orange prisms, and under the microscope as rectangular crystals (wt. 0·01 g.). Further small quantities were obtained from the mother-liquors. Finally, some paler yellow needles, m. p. 44–47° (giving a light yellow mercurichoride, m. p. 221—223°), were obtained, which after two crystallisations from light petroleum (b. p. 40—60°) had a constant m. p., 47·5—48°. Prolonged recrystallisation of the intermediate fractions finally yielded the pure orange prisms, m. p. 80—81·5° (p. 298), and the yellow needles, m. p. 47·5—48°, which were still non-homogeneous.

The orange prisms. These had a slightly stronger smell than the yellow needles and melted to a red liquid. The solutions in the usual solvents were deep orange [Found: C, 26·9; H, 1·6; S, 71·9%; *M* (in camphor), 133. $C_3H_2S_3$ requires C, 26·9; H, 1·5; S, 71·6%; *M*, 134]. With alcoholic mercuric chloride a canary-yellow mercurichloride, m. p. 218—219°, was obtained which with potassium iodide regenerated the orange prisms, unchanged in properties or m. p. (80—81·5°).

The yellow needles (Found: C, 26·9; H, 1·6; S, 72·4%; *M*, 137). With alcoholic mercuric chloride a very pale yellow mercurichloride was precipitated, m. p. 223—224°, mixed m. p. with above mercurichloride, 217—218°. With aqueous potassium iodide the non-homogeneous yellow needles were regenerated, unchanged in properties and m. p.

In other experiments M.O.S. gave a mercurichloride, m. p. 193·5—195·5° (Found: S, 23·7; Cl, 17·05. Calc. for $C_3H_2S_3Cl_2Hg$: S, 23·7; Cl, 17·5%). Its behaviour on crystallisation from acetone suggested the presence of a mixture. The specimen was clearly a monomercurichloride and the weight obtained from known amounts of the ingredients was in agreement with this view.

Isolation of Pure O.S. (I) (1 : 3-*Dithia*cyclo*pent*-4-*ene*-2-*thione*).—*Action of sodium hydroxide.* M.O.S., m. p. 44—47°, and aqueous sodium hydroxide (33%) were warmed under reflux at 100° for 5 hours. A brown oil remained, which was unaffected by more sodium hydroxide and solidified to pale yellow needles of constant m. p. 50° from alcohol and from light petroleum (b. p. 40—60°), identical with (I) (see below). The alkaline filtrate gave hydrogen sulphide and sulphur on acidification. These were removed, and the solution exactly neutralised; it then gave a black precipitate with ammoniacal silver nitrate, a red colour with ferric chloride, and decolorised bromine water, indicating the presence of a formate. Treatment of the residue, after evaporation, with cold sulphuric acid gave carbon monoxide (reduction of palladous chloride to palladium).

The pale yellow needles, m. p. 50° (0·5 g.), were again warmed under reflux for 3 hours with sodium hydroxide (3 g.) in methyl alcohol (5 ml.) and water (2 ml.). Reaction slowly occurred and a deep-red solution was formed. Acidification gave sulphur dioxide and sulphur. Formate, aldehydes, ketones, and malonate were absent.

Separation of the orange solids. M.O.S. (0·5 g.) in dry benzene (10 ml.) was passed down a column of finely powdered activated alumina (450 × 25 mm.), suspended in dry benzene, and the lowest, yellow, band was easily eluted with benzene. Removal of the benzene (reduced pressure) gave (I) (0·3 g.), which crystallised from alcohol in pale yellow needles, m. p. 50° (constant). The middle band was eluted with acetone, and yielded 1 : 2-*dithia*cyclo*pent*-4-*ene*-3-*thione* (II) (0·1 g.), which crystallised in orange prisms, constant m. p. 82°, from alcohol (see above). [Found, for (I): C, 26·8; H, 1·75; S, 71·7%; *M*, cryoscopic in benzene, 125. Found, for (II): C, 27·1, H, 2·2; S, 71·05%; *M*, 130. $C_3H_2S_3$ requires C, 26·9; H, 1·5; S, 71·6%; *M*, 134]. (I) darkened on exposure to light, giving a brown solid, insoluble in alcohol and acetone. It is moderately soluble in alcohol, acetone, and carbon tetrachloride; easily in benzene, chloroform, and ether; slightly in light petroleum, and very slightly in water. (II) was stable to light and of similar solubility to (I). Addition of Grote's reagent (*loc. cit.*) to (I) or (II) gave a purple colour, indicating the presence of the " thioacid group " ·S·CS·.

Reactions of (I).—(1) *Methiodide.* (I) (0·2 g.) and methyl iodide (0·5 ml.) in nitromethane (1 ml.) were left at room temperature for several hours. The yellow *methiodide*, m. p. 131—132° (decomp.), crystallised from methyl alcohol, and regenerated (I), unchanged in m. p., on treatment with pyridine (Found: I, 46·2. $C_4H_5S_3I$ requires I, 46·0%).

(2) *Mercurichlorides.* (I) (0·025 g.), mercuric chloride (0·05 g.), and alcohol (2 ml.) were shaken together. The pale yellow precipitate (0·05 g.), m. p. 191° (decomp.), was insoluble in alcohol and was presumably a monomercurichloride. Similar treatment of (I) in alcohol with excess of mercuric chloride gave a pale yellow solid (0·1 g.), m. p. 222—223° (decomp.), presumably a dimercurichloride. Both the products yielded unchanged (I), m. p. 50°, on treatment

with hydrochloric acid. The mercurichloride obtained from the M.O.S. was shown to be a monoaddition compound (see p. 298).

(3) Methyl sulphate (0·5 g.), (I) (0·2 g.), and benzene (3 ml.) were left at room temperature for two days. A pale red oil separated, but did not solidify in ice. Treatment with potassium iodide solution gave an orange solid, m. p. 127° (decomp.), not depressing the m. p. of the methiodide, m. p. 131—132° (decomp.), of (I). Repetition of the experiment with acetone (3 ml.) as solvent gave colourless crystals, m. p. 132°. These also formed the methiodide, m. p. 128° (decomp.), with potassium iodide.

(4) Silver nitrate in alcohol with (I) gave a pale yellow precipitate, m. p. 124° (decomp.), and (II) gave a deep yellow precipitate, m. p. 135° (decomp.). Both contained nitrate, shown by diphenylamine–sulphuric acid test. A monoaddition compound was indicated on analysis of the product, m. p. 100—120° (decomp.), from M.O.S. and silver nitrate (Found: Ag, 34·9. Calc. for $C_3H_2S_3,AgNO_3$: Ag, 35·5%).

(5) Cupric chloride gave a brick-red precipitate with (I) in alcohol, and a deep red precipitate with (II). Analysis of the precipitate obtained from M.O.S. indicated a monoaddition compound (Found: Cu, 24·5. Calc. for $C_3H_2S_3,CuCl_2$: Cu, 24·2%).

(6) *Neutral hydroxylamine.* (I) (0·7 g.), methyl alcohol (20 ml.), hydroxylamine hydrochloride (4·1 g.), anhydrous sodium carbonate (3·1 g.), and water (30 ml.) were heated under reflux until colourless (3 hr.). Hydrogen sulphide was freely evolved, and sulphur (0·25 g.) deposited. The solution smelled of ammonia. The methyl alcohol was removed, and the aqueous solution extracted with ether. The presence of thiosulphate in the aqueous layer was proved. The ether yielded a greenish-white solid (0·2 g.) which, crystallised five times from chloroform–methyl alcohol, gave colourless plates, m. p. 176°, containing nitrogen but no sulphur. Glyoxime has m. p. 179—180° (Found: C, 26·6; H, 4·35. Calc. for $C_2H_4O_2N_2$: C, 27·2; H, 4·55%). The product gave an orange precipitate on warming with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. Neutralisation of an aqueous solution of the glyoxime with ammonia, and treatment with silver nitrate gave a white precipitate of the silver salt.

Glyoxime was also obtained from the unseparated M.O.S. under similar conditions. Thiosulphate, hydrogen sulphide, and sulphur were recognised as before. The glyoxime had m. p. and mixed m. p. 179—180° with an authentic specimen, m. p. 179—180° [Found: C, 27·7; H, 4·85%; *M* (in camphor), 98·5, 98. Calc. for $C_2H_4O_2N_2$: C, 27·2; H, 4·55%; *M*, 88]. Its properties agreed with those recorded by Ulpiani (*Gazzetta*, 1912, **42**, i, 255).

(7) *Reduction with sodium and alcohol.* (*a*) (I) (1 g.) in alcohol (25 ml.) was reduced with sodium in an atmosphere of nitrogen. Water was added, the mixture acidified, and volatile matter aspirated in nitrogen through water, 5% cadmium sulphate in N-sulphuric acid (A), mercuric cyanide (B), and mercuric chloride (C) solutions successively. A greenish-yellow precipitate was formed in (B), a yellow precipitate in (A), and a trace of a white precipitate in (C). Crystallisation of the precipitate (from B) from ethyl acetate gave white crystals, m. p. and mixed m. p. 175° with authentic bismethylthiomercury, m. p. 175° (Found: S, 21·4. Calc. for $C_2H_6S_2Hg$: S, 21·7%). A portion of (B) was insoluble in ethyl acetate, did not melt below 300°, and gave the odour of ethane-1 : 2-dithiol with dilute hydrochloric acid (see below). It presumably also contained a compound of the type $Hg(SMe)_2,HgS$ which is yellow.

(*b*) (I) (4 g.) in alcohol (100 ml.) was reduced with sodium in a nitrogen atmosphere, with cooling in ice. The red solution on acidification gave hydrogen sulphide and a thiol, which was purified by extraction with ether, solution in alkali, and subsequent acidification and distillation. It had b. p. 140—150°, and gave a white precipitate with mercuric cyanide, which was unmelted below 300°, and could not be purified; it gave a yellow amorphous derivative with chloro-2 : 4-dinitrobenzene (see p. 294), m. p. 200—230°, which crystallised to constant m. p. 244° from glacial acetic acid (Found: C, 39·7; H, 2·6; S, 15·11. Calc. for $C_{14}H_{10}O_8N_4S_2$: C, 39·5; H, 2·35; S, 15·05%). The derivative did not depress the m. p. of an authentic specimen of the 1 : 2-bis-(2 : 4-dinitrophenylthio)ethane, m. p. 245° (see above) (Bost, Turner, and Conn, *J. Amer. Chem. Soc.*, 1933, **55**, 4956, give m. p. 248°). Ethanedithiol was prepared by Meyer's method.

(8) *Reduction.* (i) With lithium aluminium hydride. (I) (0·2 g.), lithium aluminium hydride (0·5 g.), and dry ether (30 ml.) were warmed under reflux until colourless (30 min.). Cautious decomposition with ice-water, acidification, and extraction with ether gave a thiol. Conversion into the 2 : 4-dinitrophenyl sulphide with sodium hydroxide and chloro-2 : 4-dinitrobenzene (Bost, Turner, and Norton, *ibid.*, 1932, **54**, 1985) gave a yellow solid, m. p. 240° after four crystallisations from glacial acetic acid. Further purification was not carried out, but the derivative again gave no depression in m. p. when mixed with that of ethane-1 : 2-dithiol (Found: C, 39·9; H, 3·1%).

(ii) With zinc and acetic acid. (I) (0·3 g.) in glacial acetic acid was heated under reflux with zinc dust until the solution was colourless (30 min.). Hydrogen sulphide was evolved. Steam-distillation yielded initially a trace of a volatile sulphur compound (Z) which gave no precipitate with mercuric cyanide solution and was therefore not a thiol. A white precipitate was obtained with mercuric chloride solution, indicating a sulphide or a disulphide, and this darkened at 115° on heating but did not melt. Further steam-distillation gave a greyish-white solid, m. p. 150—151° after two crystallisations from light petroleum (b. p. 40—60°). This gave no reaction with mercuric chloride, lead acetate, or aniline.

The greyish-white *substance* was also obtained by a similar reduction of M.O.S. (p. 296), and had m. p. 149—150° after similar crystallisation [Found: C, 35·1, 35·2; H, 3·1, 3·2; S, 62·0, 61·8%; *M* (in camphor), 243. $(C_3H_3S_2)_2$ requires C, 35·0; H, 2·9; S, 62·1%; *M*, 206]. The solid gave no methiodide and no reaction with neutral hydroxylamine. It was oxidised by neutral potassium permanganate but no sulphate was formed.

Further reduction of the solid with zinc and glacial acetic acid gave hydrogen sulphide, some unchanged material, and a small amount of the volatile sulphur compound (Z).

(iii) Reduction with hydrogen and Raney nickel. (I) (0·5283 g.), Raney nickel (2 g.), and alcohol (25 ml.) were shaken in hydrogen for 3 days, a further 2 g. of nickel (total 10 g.) being added each time the absorption of hydrogen ceased. 390 Ml. of hydrogen were absorbed (8H per molecule; the amount theoretically required for production of nickel sulphide, ethane, and methane). The recovered catalyst, on treatment with hydrochloric acid gave hydrogen sulphide but no thiol or organic sulphide. The alcohol filtered from the nickel sulphide was colourless, contained no thiol or sulphide (mercuric chloride test), and yielded nothing on evaporation under reduced pressure.

(9) *Attempted catalytic hydrogenations.* (I) (0·2 g.) in alcohol (20 ml.) was shaken in hydrogen for 8 hours with: (*a*) nickel powder from nickel nitrate, (*b*) palladium chloride on gum arabic, (*c*) palladium chloride on charcoal, (*d*) Adams's platinum oxide under 4 atm. In all cases (I) was recovered in good yield, unchanged in m. p.

(10) Benzoyl peroxide (0·8 g.), (I) (0·4 g.), and light petroleum (b. p. 60—80°) (30 ml.) were heated under reflux for 2 hours. (I) was recovered unchanged on removal of the solvent and crystallisation from alcohol.

(11) *Bromination.* A solution of bromine (3 g.) in carbon tetrachloride (100 ml.) was titrated against (I) (0·1592 g.), starch–iodide paper being used. The amount of bromine required was 0·197 g. [(I) requires 0·214 g. bromine to form the dibromide]. The orange dibromide (yield 90%), m. p. 147° (decomp.), with cold water, regenerated (I) in almost theoretical yield. When heated, it decomposed to hydrogen bromide and a black insoluble solid, which could not be purified.

(12) *Attempted Diels–Alder reaction.* (I) (0·2 g.), anthracene (0·1 g.), and dry benzene (3 ml.) were heated under reflux for 3 hours and left overnight. Both ingredients were recovered unchanged on crystallisation from alcohol.

(13) *Fission of the ring of* (I) *by piperidine.* (I) (0·5 g.) and piperidine (excess) were heated at 100° for 2 hours. Addition of acetone (5 ml.) gave a dark brown solid, which was crystallised from acetone to constant m. p. 164·5°, giving white crystals which were soluble in water, sublimed on heating, and with aqueous sodium hydroxide gave the odour of piperidine [Found: C, 54·3; H, 8·9; S, 25·6. *M* (in camphor), 250. Calc. for $C_{11}H_{22}N_2S_2$: C, 53·8; H, 8·9; S, 26·0%; *M*, 246]. They did not depress the m. p. of an authentic specimen of piperidinium piperidino-1-dithiocarboxylate, m. p. 165° (Ladenburg and Roth, *Ber.*, 1884, **17**, 514). The acetone mother-liquors yielded no further product.

(14) *Mercuric acetate.* (I) (1 g.) in chloroform (20 ml.) was treated with a solution of mercuric acetate (10 g.) in glacial acetic acid (100 ml.), and left for 12 hours. The colourless solution was filtered from the white, insoluble solid (see p. 295) through a sintered-glass funnel, and the solid washed with fresh chloroform (5 ml.). The filtrate was diluted with water, the chloroform separated, and the aqueous solution extracted with chloroform (6 × 10 ml.). Distillation of the chloroform under reduced pressure yielded a pale yellow solid with a butter-like odour, m. p. 34—35° (0·4 g.), easily soluble in ether, acetone, alcohol, and chloroform, but crystallising from light petroleum (b. p. 40—60°) in white feathery crystals of constant m. p. 35° [Found: C, 30·9; H, 2·0; S, 53·8, 53·7%; *M* (in camphor), 112. $C_3H_2OS_2$ requires C, 30·5; H, 1·7; S, 54·2%; *M*, 118]. The compound appears to be 1 : 3-*dithia*cyclo*pent*-4-*ene*-2-*one* from consideration of the similar reaction with ethylene trithiocarbonate. It gave no precipitates with aqueous mercuric chloride, bromine in carbon tetrachloride, 2 : 4-dinitrophenylhydrazine, *p*-nitrophenylhydrazine, semicarbazide, or hydroxylamine in sodium acetate solution; but gave

hydrogen sulphide and a deposit of sulphur on treatment with hydroxylamine hydrochloride neutralised with aqueous sodium carbonate. It depressed the m. p. of ethylene dithiocarbonate, m. p. 35° (see p. 302).

(15) *Attempted hydrogenations of* 1:3-*dithia*cyclo*pent*-4-*ene*-2-*one*. (i) The carbonyl compound, $C_3H_2OS_2$, m. p. 35° (0·1 g.), was shaken with Adams's catalyst (0·1 g.) and methyl alcohol (2 ml.) in hydrogen (3 atm.) for 2 hours. Filtration and removal of the solvent gave unchanged material, m. p. 34° (0·05 g.). (ii) Palladium chloride (0·5 g.) on charcoal (4·5 g.) in methyl alcohol (50 ml.) was reduced with hydrogen at 3 atm., the carbonyl compound $C_3H_2OS_2$ (0·25 g.) added, and the shaking continued for 8 hours. Removal of the catalyst and the solvent gave unchanged material, m. p. and mixed m. p. 35°.

(16) *Action of potassium hydrogen sulphide* (see Husemann, *Annalen*, 1862, **123**, 89, for the action on ethylene trithiocarbonate). Potassium hydroxide (0·45 g.) in absolute alcohol (25 ml.) was treated with excess of hydrogen sulphide. (I) (0·5 g.) in alcohol (5 ml.) was added, and the mixture heated under reflux for 2 hours The orange-coloured precipitate was removed, washed with alcohol, and identified as potassium trithiocarbonate by the following reactions: (i) It was very soluble in water, giving a red solution. (ii) Excess of dilute sulphuric acid on warming gave hydrogen sulphide, sulphur, and carbon disulphide; the last was identified by extraction with ether and precipitation with phenylhydrazine; the resulting compound had m. p. 100° (decomp.), and the compound prepared from phenylhydrazine and carbon disulphide in ether (Fischer, *Annalen*, 1878, **190**, 114) had m. p. 104—105° (decomp.). (iii) Ethylene dibromide (1 g.) and aqueous alcohol (1 : 1) (2 ml.) were added to the remaining precipitate and warmed. A clear yellow solution was formed. Dilution with water, extraction with ether, and crystallisation from light petroleum (b. p. 40—60°) gave yellow crystals, m. p. and mixed m. p. 35°, with authentic ethylene trithiocarbonate.

The alcoholic solution from the reaction gave a thiol, on dilution with water and acidification, which was extracted with ether, and the extract washed with 5% cadmium sulphate in N-sulphuric acid to remove hydrogen sulphide. A portion was shaken with mercuric cyanide solution, the ether removed, and the white mercury salt, m. p. 135—136° (decomp.), filtered off. It was only slightly soluble in alcohol, ethyl acetate, and acetone, and could not be crystallised.

To the remainder of the thiol in ether, alcohol (10 ml.), aqueous sodium hydroxide (1 ml., 10%), and chloro-2 : 4-dinitrobenzene (0·5 g.) in alcohol (10 ml.) were added. Heating under reflux for 20 minutes gave a yellow solid, which was slightly soluble in alcohol and glacial acetic acid. Washed with water and alcohol, it had m. p. 185° (Found: C, 40·0; H, 2·3; N, 12·6; S, 14·95. $C_{14}H_8O_8N_4S_2^*$ requires C, 39·7; H, 1·9; N, 13·2; S, 15·1%). The m. p.s of 1 : 2-di-(2 : 4-dinitrophenylthio)ethane, m. p. 245°, and 1 : 3-di-(2 : 4-dinitrophenylthio)propane, m. p. 192°, were depressed to 160—170° and 175—177° respectively, on mixing with the above derivative.

Reactions of (II), *m. p.* 82°.—(1) A specimen of (II) did not depress the m. p. of "propylene trithione," m. p. 82° (see p. 304), prepared from propylene and sulphur.

(2) *Mercurichloride*. (II) (0·05 g.) in alcohol (1 ml.) was treated with mercuric chloride solution. The pale yellow precipitate had m. p. 218—219° (decomp.), after washing with water and alcohol, and did not depress the m. p. of the mercurichloride of "propylene trithione" (see p. 297).

(3) *Methiodide*. (II) (0·05 g.) with methyl iodide (0·1 g.) in nitromethane (2 ml.) gave an orange addition product, m. p. 175° (decomp.), not depressing the m. p. of the *methiodide* of "propylene trithione" (see p. 304) (Found: C, 17·55; H, 1·85; I, 46·0. $C_4H_5S_3I$ requires C, 17·4; H, 1·80; I, 46·0%).

(4) and (5) Hydroxylamine hydrochloride with aqueous sodium acetate (4) or sodium carbonate (5) gave no oxime. With (5), on warming, thiosulphate but no free sulphur was obtained.

(6) Reduction with sodium and alcohol of (II) (2 g.) gave a red solution, becoming black on further reduction. The thiol, isolated as usual, was treated with chloro-2 : 4-dinitrobenzene, but no derivative was obtained.

(7) *Action of triphenylphosphine*. (II) (0·1 g.) in ethyl acetate (5 ml.) was heated under reflux for 2 hours with triphenylphosphine. Filtration from a brown, insoluble solid (A) yielded a solid which formed white crystals from alcohol, m. p. 158° (Found: C, 73·8; H, 5·15. Calc. for $C_{18}H_{15}SP$: C, 73·5; H, 5·3%). They contained sulphur and did not depress the m. p. of authentic triphenylphosphine sulphide, m. p. 158°, but depressed that of triphenylphosphine oxide (m. p. 154°) to 123°. The brown addition *compound* (A) also contained sulphur and decomposed on heating to a black residue, and evolved the odour of (II) (Found: C, 64·2; H, 4·6. $C_3H_2S_3.C_{18}H_{15}P$ requires C, 63·7; H, 4·3%).

Reactions of Ethylene Trithiocarbonate, m. p. 36°.—This was prepared in 60% yield according to Husemann (*loc. cit.*).

Reduction with sodium and alcohol. Ethylene trithiocarbonate was reduced with sodium and alcohol. The colourless solution was diluted with water and acidified, and volatile products were aspirated with nitrogen successively through 5% cadmium sulphate in N-sulphuric acid, sodium acetate, and mercuric cyanide solutions. The cadmium sulphide formed corresponded to 28% of the sulphur content of the trithiocarbonate. Traces of a mercury mercaptide were obtained which was insoluble in ethyl acetate and infusible but gave the odour of ethane-1 : 2-dithiol with dilute hydrochloric acid. No methanethiol was detected. Extraction of the aspirated solution with ether yielded ethanedithiol. Treatment with chloro-2 : 4-dinitrobenzene as before (p. 299) gave a yellow derivative, m. p. 245°, after four crystallisations from glacial acetic acid; mixed m. p. 245° with authentic 1 : 2-di-(2 : 4-dinitrophenylthio)ethane (Found : C, 39·2; H, 2·3; N, 13·2; S, 15·15. Calc. for $C_{14}H_{10}O_8N_4S_2$: C, 39·5; H, 2·35; N, 13·1; S, 15·05%).

Attempted dehydrogenation of ethylene trithiocarbonate. (*a*) Ethylene trithiocarbonate was not dehydrogenated by palladium powder in benzene or in absence of a solvent or palladium on charcoal in mesitylene or freshly reduced nickel powder in benzene. (*b*) Dehydrogenation was not effected by sulphur or selenium at 200°. (*c*) Tetrachlorobenzoquinone or benzoquinone in boiling xylene, or selenium dioxide in aqueous dioxan or aqueous acetic acid at 100°, or lead tetra-acetate in glacial acetic acid at room temperature, failed to dehydrogenate the trithiocarbonate. (*d*) Ethylene trithiocarbonate (10 g.) and carbon dioxide were passed through a Pyrex tube 24″ long, loosely packed with catalytic nickel prepared from nickel nitrate (40 g.) on porous pot (200 g.) at 320°. Extraction of the distillate and of the catalyst with acetone gave only unchanged ester (6 g.), m. p. 35°.

Action of mercuric acetate. The acetate (5 g.) in glacial acetic acid (100 ml.) was added to ethylene trithiocarbonate (2 g.) in chloroform (20 ml.). The yellow colour was discharged in 2—3 minutes and a white solid (A) was deposited. After 2 hours the mixture was filtered, and the filtrate diluted with water and extracted several times with chloroform. The aqueous layer contained no sulphate. The chloroform yielded a colourless oil which solidified in ice to a white solid, m. p. 33—34° (1·1 g.), and was crystallised from light petroleum (b. p. 40—60°) to constant m. p. 35° [Found : C, 30·3; H, 3·7; S, 53·4%; *M* (in camphor), 117. Calc. for $C_3H_4OS_2$: C, 30·0; H, 3·3; S, 53·3%; *M*, 120]. The crystals obtained in a yield of 62% did not depress the m. p. of ethylene dithiocarbonate, m. p. 35°, prepared from dilute nitric acid and ethylene trithiocarbonate (Husemann, *Annalen*, **1863**, **126**, 269). No derivative was obtained with 2 : 4-dinitrophenylhydrazine, *p*-nitrophenylhydrazine, or mercuric chloride. Bromine in carbon tetrachloride was unaffected, but bromine water was decolorised. An oxime, m. p. 126—128°, was obtained with hydroxylamine hydrochloride neutralised with sodium carbonate. This did not depress the m. p. of the oxime (3-oximino-1 : 2-dithia*cyclo*pentane) obtained from ethylene trithiocarbonate and neutral hydroxylamine (Miolati, *Annalen*, 1891, **262**, 78).

The white solid (A) blackened when heated, and darkened slightly when boiled for a long time with dilute nitric acid. With aqueous sodium thiosulphate it became orange, then red and finally black. Potassium iodide gave similar results on warming, and potassium mercuric iodide was detected in the solution. With hydrogen sulphide (A) became black. It was not mercurous acetate. Aqueous potassium hydroxide yielded initially an orange colour, quickly becoming red, and finally a black precipitate (B) which was insoluble in hot nitric or hydrochloric acids but completely soluble in aqua regia, leaving sulphur; in boiling fuming nitric acid (B) gave a white solid which became yellow and finally black again when heated with aqueous potassium hydroxide.

The white compound $HgS,Hg(OAc)_2$ was prepared by passing hydrogen sulphide into excess of mercuric acetate solution with shaking. It gave exactly similar reactions to (A), including the transient orange and red colours with aqueous potassium hydroxide. These colours are not given by the compound $2HgS,HgCl_2$, only black 2HgS,HgO being obtained.

Action of piperidine. Piperidine (2 g.) and ethylene trithiocarbonate (0·5 g.) were heated together at 100° for 2 hours. Acetone (2 ml.) was added, yielding a white solid, m. p. 204—205°, separating from benzene in colourless crystals. After five crystallisations the m. p. was constant at 212° (Solid A). The acetone extract yielded greyish-white crystals, m. p. 164° (decomp.), and more were recovered from the benzene mother-liquors of Solid A. After crystallisation from acetone, the crystals were colourless and had the constant m. p. 164·5° (decomp.). These contained sulphur and nitrogen, were soluble in water, and gave piperidine on heating or with cold aqueous sodium hydroxide [Found : C, 54·0; H, 8·75; S, 25·7%; *M* (in camphor), 234.

Calc. for $C_{11}H_{22}N_2S_2$: C, 53·8; H, 8·9; S, 26·0%; *M*, 246]. No depression in m. p. was obtained with piperidinium piperidino-1-dithiocarboxylate (see p. 300).

Solid A contained nitrogen and sulphur and was insoluble in water. Sodium hydroxide gave no piperidine. When heated, it finally decomposed leaving no residue. Boiling lead acetate or mercuric chloride solution gave no precipitate. Aniline on boiling gave hydrogen sulphide, indicating the thioketonic group. Bromine in chloroform yielded an insoluble, orange addition *product*, unstable to water [Found: C, 50·8; H, 7·15; S, 34·8%; *M* (in camphor), 374. $C_{16}H_{28}N_2S_4$ requires C, 51·0; H, 7·45; S, 34·1%; *M*, 376].

Ethylene trithiocarbonate dibromide. (i) Titration of ethylene trithiocarbonate (0·18 g.) in carbon tetrachloride (5 ml.) with bromine (3 g.) in carbon tetrachloride (100 ml.), with use of starch–iodide paper, indicated the absorption of 2 atoms of bromine.

(ii) Bromine (12 g.) in chloroform (25 ml.) was added slowly with shaking to ethylene trithiocarbonate (10 g.) in chloroform (50 ml.). After 2 hours the orange-yellow dibromide was filtered off, washed with chloroform, and stored in absence of air (yield 20 g.). It had m. p. 120°. It was decomposed by water or moist air, regenerating the ester [compare analogous behaviour of the dibromide of (I), p. 300].

Action of pyridine. The dibromide (0·5 g.), pyridine (0·5 ml.), and dry ether (or alcohol; 5 ml.) were left for 8 hours. The dibromide slowly dissolved, giving a yellow solution. The solvent was removed, and the yellow residue washed with dilute hydrochloric acid and crystallised from alcohol, giving ethylene trithiocarbonate, m. p. and mixed m. p. 35—36°.

Thermal decomposition. The dibromide (20 g.) was heated in a slow stream of nitrogen at 110° for 2 days. Hydrogen bromide was evolved and precipitated as silver bromide (3·9 g., = 1·6 g. of HBr). A faint odour of carbon disulphide was noticed after removal of the hydrogen bromide. Distillation yielded a pale red oil, b. p. 130°, and extraction of the residue with carbon disulphide gave free sulphur. The oil was washed with water and distilled in steam, giving 6·90 g. of a colourless oil, b. p. 127°/731 mm., f. p. 9—10°, proved to be ethylene dibromide (b. p. 129°, f. p. 10°). This conclusion was confirmed by heating the oil with thiourea and treatment of the resulting di*iso*thiuronium bromide with picric acid. The picrate, m. p. 258° (decomp.), did not depress the m. p. of the derivative obtained from authentic ethylene dibromide, m. p. 259° (decomp.) (Levy and Campbell, *J.*, 1939, 1442, give m. p. 260°). The oil also gave a β-naphthyl ether on heating under reflux with β-naphthol; this was crystallised to m. p. 208° from alcohol–water, and did not depress the m. p. of authentic 1 : 2-di-β-naphthyloxyethane, m. p. 209—210°.

Attempted Synthesis of (I) (1 : 3-*Dithio*cyclo*pent*-4-*ene*-2-*thione*).—*cis*-Dichloroethylene, *cis*-dibromoethylene, and an unseparated mixture of *cis*- and *trans*-dibromoethylene were treated with potassium trithiocarbonate in various solvents at room temperature, at 60°, 70°, or 80° or without a solvent in a sealed tube at 180°, but no formation of (I) could be detected. Di-iodoethylene (Keiser, *Amer. Chem. J.*, 1899, **21**, 263) did not react with the trithiocarbonate in boiling alcohol.

Action of tetrabromoethane on sodium trithiocarbonate. Tetrabromoethane (34·6 g.) and sodium trithiocarbonate (15·4 g.) in alcohol (40 ml.) were heated under reflux for 1 hour. Hydrogen sulphide was evolved and sulphur deposited. Dilution with water and distillation in steam gave 4 g. of dibromoethylene, b. p. 108—110°, since, on treatment with bromine (8 g.) and water (40 ml.) and distillation in steam, tetrabromoethane, b. p. 202° (decomp.), was obtained.

Reduction of diethyl trithiocarbonate. The ester (4 g.) in alcohol (50 ml.) was reduced with sodium. Dilution with water and acidification gave a thiol, which was extracted with ether. The 2 : 4-dinitrophenyl sulphide, prepared in the usual manner, formed pale yellow crystals (from alcohol), m. p. 113·5°, not depressing the m. p. of an authentic specimen prepared from ethanethiol, m. p. 114° (Bost, Turner, and Norton, *loc. cit.*, give m. p. 115°).

Reduction of 1 : 3-*Dithiolan with Sodium and Alcohol.*—1 : 3-Dithiolan (1 g.) in alcohol (15 ml.) was reduced with sodium. Dilution with water and acidification gave a thiol on extraction with ether. The corresponding 2 : 4-dinitrophenyl sulphide formed pale yellow needles from alcohol, m. p. 81° (Found: C, 39·45; H, 3·55; N, 10·3; S, 23·15. $C_9H_{10}O_4N_2S_2$ requires C, 39·4; H, 3·6; N, 10·4; S, 23·25%). The mixed m. p. with an authentic specimen of 1-(2 : 4-*dinitrophenylthio*)-2-*methylthioethane* (m. p. 81·5°) was 81°.

Action of Sulphur on 1 : 3-*Dithiolan.*—Sulphur (5 g.) and 1 : 3-dithiolan (2 g.) were heated under reflux at 200—230° for 4 hours. Hydrogen sulphide was freely evolved, and a red solid formed on cooling. Extraction with hot alcohol and removal of the solvent and unchanged sulphur gave a yellow solid, which crystallised from alcohol to constant m. p. 36°, not depressing the m. p. of authentic ethylene trithiocarbonate. It gave a white precipitate, m. p. 166°, with

mercuric chloride solution, and an orange precipitate, m. p. 118°, with bromine in chloroform. Ethylene trithiocarbonate behaves in a similar manner.

Preparation of Reference Compounds.—(1) Dimethyl trithiocarbonate, prepared in 60% yield from sodium trithiocarbonate and methyl iodide in alcohol, had b. p. 92°/13 mm. (207°/752 mm.), f. p. −3° (Cahours, *Ann. Chim.*, 1847, **19**, 162, gives b. p. 204—205°).

(2) Diethyl trithiocarbonate, prepared similarly (yield 62%), had b. p. 113°/11 mm., f. p. −12° (Husemann, *Annalen*, 1862, **123**, 67, gives b. p. 240°).

(3) Propylene trithiocarbonate was prepared from propylene dibromide and sodium trithiocarbonate by Husemann's method (*ibid.*, 1863, **126**, 295) in 60% yield; b. p. 157°/10 mm. (Found: S, 63·7. Calc. for $C_4H_6S_3$: S, 64·0%).

(4) Methyl dithiopropionate, $CH_3{\cdot}CH_2{\cdot}CS{\cdot}SMe$, prepared according to Houben and Schultze (*Ber.*, 1910, **43**, 2483, who give b. p. 92—93°/70 mm.), was an orange oil, b. p. 83°/22 mm.

(5) 1 : 3-Dithiolan was obtained as a colourless oil, b. p. 67°/14 mm., from ethanedithiol and formaldehyde in 30% yield (Gibson, *J.*, 1930, 13, gives b. p. 61°/11 mm.). Mercuric chloride solution gave a white precipitate which crystallised from alcohol in colourless needles, m. p. 126° (Gibson gives m. p. 119°) (Found: Cl, 18·4. Calc. for $C_3H_6S_2Cl_2Hg$: Cl, 18·8%).

(6) 2-Methylthioethanethiol, $CH_3{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}SH$, was obtained in 60% yield, b. p. 74·5°/34 mm., from ethylene sulphide and sodium methyl sulphide (Meade and Woodward, *J.*, 1948, 1894, give b. p. 82°/40 mm.).

The thiol (1 g.), alcohol (10 ml.), 10% sodium hydroxide solution (4 ml.), and chloro-2 : 4-dinitrobenzene (2 g.) in alcohol (5 ml.) were heated under reflux for 10 minutes. Cooling gave 1-(2 : 4-*dinitrophenylthio*)-2-*methylthioethane*, which crystallised in yellow needles from alcohol, m. p. 81·5° (Found: C, 39·4; H, 3·5; N, 10·25; S, 23·0. $C_9H_{10}O_4N_2S_2$ requires C, 39·4; H, 3·6; N, 10·2; S, 23·25%).

The thiol (0·5 g.), treated in a similar manner with *p*-chloronitrobenzene (1 g.), afforded the *p-nitrophenyl sulphide*, which separated as an oil which solidified in ice, and crystallised from alcohol or light petroleum (b. p. 40—60°) in yellow needles, m. p. 34·5° (Found: C, 47·25; H, 4·9; N, 5·9. $C_9H_{11}O_2NS_2$ requires C, 47·2; H, 4·8; N, 6·1%).

The thiol, on treatment with alcoholic mercuric cyanide gave a white precipitate, which separated from alcohol as colourless crystals of *bis*-2-*methylthioethylthiomercury*, m. p. 104·5° (Found: Hg, 47·6. $C_6H_{14}S_4Hg$ requires Hg, 48·3%).

(7) 2-Methyl-1 : 3-dithiolan was prepared by Fasbender's method (*Ber.*, 1888, **21**, 1475) from ethane-1 : 2-dithiol and acetaldehyde. The colourless oil, b. p. 58°/12 mm. (lit., b. p. 172—173°), darkened when kept. The white addition *compound* with mercuric chloride was sparingly soluble in alcohol or ethyl acetate, and did not melt when heated (Found: Cl, 18·15. $C_4H_8S_2Cl_2Hg$ requires Cl, 18·15%).

(8) "*Propylene trithione*" (1 : 2-*dithia*cyclo*pent*-4-*ene*-3-*thione*). The apparatus and procedure were essentially the same as described by Lüttringhaus, König, and Böttcher (*Annalen*, 1948, **560**, 211). Propylene was passed for 8 hours through a Pyrex tube containing crushed sulphur (150 g.) at 240°. The product was purified by steam-distillation and chromatographic separation in benzene on active alumina. Crystallisation of the product from alcohol gave orange prisms (0·2 g.), m. p. 82° (the authors give m. p. 82°), mixed m. p. 82° with (II). The mercuric chloride addition product was pale yellow, m. p. 218—219° (decomp.), mixed m. p. 218—219° (decomp.) with the derivative of (II) of the same m. p. The methiodide was orange, m. p. 173—174° (decomp.), mixed m. p. 174—175° (decomp.) with the methiodide of (II) (see p. 301) of the same m. p.

We are much indebted to Professor R. Mecke, of the University of Freiburg, for measuring the infra-red spectra of (I), (II), and ethylene trithiocarbonate, to Drs. J. Bruce and W. E. Allenby for assistance in the early stages of this research, and to the Ministry of Education for an F.E.T.S. grant to E. A. M.

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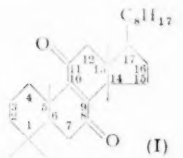
61. *Lanosterol. Part XV.* Some Reactions of Hydrocarbons of the Lanosterol Series.*

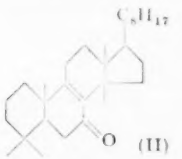
By J. F. McGhie, M. K. Pradhan, and W. A. Ross.

Oxidation of lanostene and γ-lanostadiene with chromic acid, or of γ-lanostadiene with perbenzoic acid, gave lanosten-8-one. Dehydrogenation of this ketone with selenium dioxide yielded lanostatrienone, which on chromic acid oxidation gave lanostadienetrione, also obtained by oxidation of lanostenedione with selenium dioxide. The presence of an α-diketone grouping in lanostadienetrione was shown by oxidation with alkaline hydrogen peroxide to a dicarboxylic acid.

Lanostanedione on oxidation with selenium dioxide gave lanost-6-ene-8 : 11-dione. Lanostanedione when reduced by the modified Wolff–Kishner procedure gave lanostan-11-one, and with lithium aluminium hydride followed by acetylation gave 8-acetoxylanostan-11-ol, dehydrated by phosphorus oxychloride to lanost-10-en-8-yl acetate.

In recent work on lanostadienyl acetate and its derivatives (*J.*, 1952, 3176, and earlier papers) we have reported numerous nuclear oxidation products, such as keto- and diketo-lanostenyl acetate and triketolanostadienyl acetate, and these compounds have in some cases been reduced further to the corresponding saturated compounds. We now report parallel experiments with the hydrocarbons, lanostadiene (McGhie, Pradhan, and Cavalla, *J.*, 1952, 3176), lanostene (Petrow, Thesis, London, 1935; Ruzicka, Rey, and Muhr, *Helv. Chim. Acta*, 1944, **27**, 472; Wieland and Joost, *Annalen*, 1941, **546**, 119; Dorée, McGhie, and Kurzer, *J.*, 1947, 1467), and γ-lanostadiene (Ruzicka *et al.*, *loc. cit.*; Dorée, McGhie, and Kurzer, *J.*, 1948, 988). Oxidation of lanostene and γ-lanostadiene with chromic acid to lanost-9-ene-8 : 11-dione (I) has been described by Dorée *et al.* (*loc. cit.*; cf. Roth and Jeger, *Helv. Chim. Acta*, 1949, **32**, 1620); the ultra-violet absorption of this dione shows the system –CO·C:C·CO– to be fully transoid (Campbell and Harris, *J. Amer. Chem. Soc.*, 1941, **63**, 2721; Barton, Fawcett, and Thomas, *J.*, 1951, 3147).


(I)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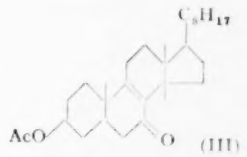
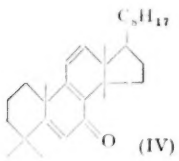

(III)

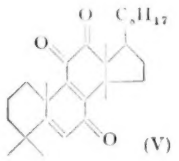
Under the conditions used for conversion of lanostenyl acetate into 8-ketolanost-9-en-2-yl acetate (III) (Marker, Wittle, and Mixon, *J. Amer. Chem. Soc.*, 1937, **59**, 1368; Ruzicka, Rey, and Muhr, *loc. cit.*; Birchenough and McGhie, *J.*, 1950, 1249) lanostene and chromic acid afford lanost-9-en-8-one (II) in poor yield; the ultra-violet absorption spectrum [max. at 255 mμ (log ε 3·97)] identifies the product as an αβ-unsaturated ketone, which is formulated as (II) by analogy with the corresponding acetoxy-compound (Barton, Fawcett, and Thomas, *loc. cit.*). Similar oxidation of γ-lanostadiene (cf. Cavalla and McGhie, *J.*, 1951, 744) also gave lanost-9-en-8-one, again in poor yield. An alternative route was tried. Birchenough and McGhie (*loc. cit.*) obtained ketolanostenyl acetate (III) by perbenzoic acid oxidation of γ-lanostadienyl acetate, but with the hydrocarbon this method gave only a glass, which was assumed to be an epoxide as it very readily rearranged, in boiling acetic acid containing a drop of sulphuric acid, to lanost-9-en-8-one.

Experiments similar to those described for ketolanostenyl acetate (Cavalla and McGhie, *loc. cit.*) were carried out on lanost-9-en-8-one (II). Dehydrogenation with selenium dioxide gave a trienone, formulated as (IV) since, like the trienyl acetate (Cavalla and McGhie, *loc.*

* Part XIV, *J.*, 1952, 3176.

cit.; Barron *et al.*, *loc. cit.*), it is smoothly oxidised to the dienetrione (V). Oxidation of diketolanost-9-ene-8 : 11-dione (I) with selenium dioxide to the same dienetrione lends support to formula (V). The presence of an α-diketone grouping in (V) was confirmed by fission to a dicarboxylic acid, $C_{30}H_{46}O_5$, by alkaline hydrogen peroxide. The absorption maximum at 248 mμ suggests the presence of the system >C:C·CO·C:C·CO_2H. From this, and by analogy with the hydroxyketo-dicarboxylic acid (Cavalla and McGhie, *loc. cit.*; Barton, Fawcett, and Thomas, *loc. cit.*), the acid from (V) may be represented by (VI).


(IV)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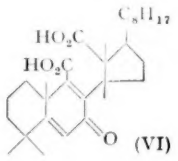
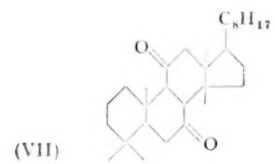

(VI)

Lanost-9-en-8 : 11-diene may be more readily obtained from *iso*cholesterol itself. Oxidation of *iso*cholesterol with Kiliani's chromic acid mixture (McGhie, Thesis, London, 1947) gave a mixture of ketones, reduced by the modified Wolff–Kishner procedure to a mixture of hydrocarbons, which on chromic acid oxidation gave lanostenedione and the trisnor-acid. Voser *et al.* (*Helv. Chim. Acta*, 1951, **34**, 1585) recently reported similar findings.

Lanostane-8 : 11-dione (VII) (Dorée, McGhie, and Kurzer, *loc. cit.*) and selenium dioxide gave a product for which formula (VIII) is suggested on the basis of the ultra-violet absorption spectrum (typical of a disubstituted αβ-unsaturated ketone) and by analogy with acetoxylanost-6-enedione (Cavalla, Thesis, London, 1951; Dorée, McGhie, and Kurzer, *J.*, 1949, 570).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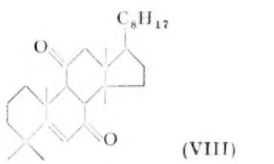
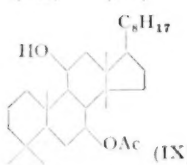
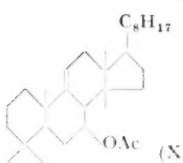
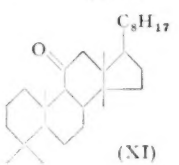

(VIII)


(IX)


(X)


(XI)

Reduction of lanostanedione with lithium aluminium hydride gave the diol (not isolated) and thence a monoacetate alcohol (IX). According to Shoppee and Sumners (*J.*, 1950, 680), reduction of sterically hindered ketones with lithium aluminium hydride gives the compound with a polar hydroxyl group. Further, Barton and Holness (*J.*, 1952, 78) have shown that polar hydroxyl groups cannot be acetylated under normal conditions. Previous evidence (Barton, Fawcett, and Thomas, and Voser *et al.*, *locc. cit.*) has indicated the more sterically hindered nature of the $C_{(11)}$-ketone group in acetoxylanostanedione and, by analogy supported by some experimental evidence (*e.g.*, formation of a mono-2 : 4-dinitrophenylhydrazone only), the $C_{(11)}$-ketone group in lanostanedione may be considered the more sterically hindered. Reduction of this to give a polar hydroxyl group at $C_{(11)}$ explains the formation of the monoacetate only. The polar nature of the hydroxyl group at $C_{(11)}$ is confirmed by ready dehydration of this compound by phosphorus oxychloride to lanost-10-en-8-yl acetate (X). Lanostanedione (VII) was also reduced by the modified Wolff–Kishner procedure to lanostan-11-one (XI), this providing further evidence for the more sterically hindered nature of the $C_{(11)}$ ketone group.

Experimental

M. p.s are uncorrected. Specific rotations were determined in chloroform solution at 20°. The aluminium oxide used in chromatographic work was from Messrs. Peter Spence Ltd. (Grade "H"). Light petroleum refers to the fraction of b. p. 60—80°. Analyses are by Drs. Weiler and Strauss, Oxford. Ultra-violet absorption spectra were measured in absolute ethanol, with a Unicam S.P. 500 spectrophotometer. The phrase " in the usual way " refers to dilution with water, extraction with ether, washing successively with aqueous sodium hydroxide, aqueous hydrochloric acid, and water, drying of the ethereal solution (Na_2SO_4), and removal of the solvent *in vacuo*.

Oxidation of γ-Lanostadiene with Chromic Acid.—γ-Lanostadiene (1·0 g.) in glacial acetic acid (40 ml.) was treated at 95° with a solution of chromic acid (0·25 g.) in 90% acetic acid (2·5 ml.) for 2 min. The reaction mixture was poured into water, and the excess of chromic acid was destroyed with dilute sulphurous acid. The precipitated solid was taken up in ether and the solution was washed with water, dilute sodium carbonate solution, and water again, until neutral. Removal of the dried (Na_2SO_4) solvent left a yellow oil, which was adsorbed on alumina (15 × 1·3 cm.) from light petroleum. Elution with light petroleum (300 ml.) and crystallisation from acetone–methanol gave plates (0·05 g.) of *lanosten-8-one*, m. p. 120°, $[\alpha]_D$ + 31·3° (*c*, 2·24), $\lambda_{max.}$ 255 mμ, log ε 3·97 (Found: C, 84·7; H, 11·7. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%). Lanostene was oxidised by the same method to lanosten-8-one.

Oxidation of γ-Lanostadiene with Perbenzoic Acid.—A solution of γ-lanostadiene (4·5 g.) in ice-cold chloroform (50 ml.) was treated at 0° with a chloroform solution of perbenzoic acid (equivalent to 0·28 g. of active oxygen). After 46 hr. the excess of the oxidising agent was destroyed by the addition of a solution of potassium iodide. The mixture was acidified and the iodine removed by shaking with 0·1N-sodium thiosulphate. The chloroform solution was washed twice with 2N-sodium hydroxide, and water until neutral, then dried (Na_2SO_4), and finally the solvent was removed *in vacuo*. The resulting oil was chromatographed in benzene on alumina (5 × 1·3 cm.). The eluates gave a glassy oil, which was heated under reflux with acetic acid (50 ml.) and concentrated sulphuric acid (2 ml.) for 10 minutes and then worked up in the usual way. An oil was obtained, which on crystallisation from acetone–methanol gave a powder (2·7 g.), m. p. 86—90°. Rechromatography, elution with light petroleum (200 ml.) and light petroleum–benzene (1 : 1) (100 ml.), and recrystallisation from acetone–methanol gave plates (1·09 g.) of lanost-9-en-8-one, m. p. (and mixed m. p.) 119—120°, $[\alpha]_D$ + 31·0° (*c*, 1·04) (Found: C, 84·5; H, 11·6. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%).

Action of Selenium Dioxide on Lanosten-8-one.—Lanosten-8-one (500 mg.) in acetic acid (50 ml.) was heated under reflux for 3 hr. with a solution of selenium dioxide (500 mg.) in water (1 ml.). The precipitated selenium was filtered off and the filtrate worked up in the usual way. A solid was obtained which was absorbed on alumina (7 × 1·3 cm.) from light petroleum. Elution with light petroleum–benzene (1 : 1) (300 ml.) and crystallisation from methanol gave needles (300 mg.) of *lanostatrienone*, m. p. 158—159°, $[\alpha]_D$ +106° (*c*, 1·18), $\lambda_{max.}$ 262 and 325 mμ, log ε 3·87 and 3·91 respectively (Found: C, 85·7; H, 10·9. $C_{30}H_{46}O$ requires C, 85·3; H, 11·0%).

Oxidation of Lanostatrienone with Chromic Acid.—Lanostatrienone (600 mg.) in glacial acetic acid (50 ml.) was treated at 95° with a solution of chromic acid (600 mg.) in 90% acetic acid (6 ml.) for 90 minutes, then worked up as in a previous similar oxidation. The orange oil obtained, on crystallisation from methanol, gave orange needles (350 mg.) of *lanostadienetrione*, m. p. 128°, $[\alpha]_D$ −52° (*c*, 3·19), $\lambda_{max.}$ 211—214 and 286 mμ, log ε 3·99 (Found: C, 79·5; H, 9·6. $C_{30}H_{44}O_3$ requires C, 79·6; H, 9·8%).

Action of Selenium Dioxide on Lanostenedione.—The dione (6·0 g.) was added to a suspension of selenium dioxide (6·0 g.) in acetic acid–acetic anhydride (1 : 1) (200 ml.), and the mixture heated under reflux for 3·5 hr. The precipitated selenium was filtered off and the filtrate concentrated *in vacuo* to a red oil. This was adsorbed on alumina (12 × 1·3 cm.) from light petroleum (with difficulty). Elution with light petroleum (200 ml.) gave a red oil, which was dissolved in ethyl acetate and cooled to −30°, whereupon a semi-solid was obtained. This was rechromatographed on alumina and elution gave the following fractions, each recrystallised from methanol: (i) light petroleum (300 ml.), amorphous orange powder (1·2 g.), m. p. 96—100°; (ii) light petroleum–benzene (1 : 1) (200 ml.), orange needles of lanostadienetrione (0·5 g.), m. p. 126—128°. Rechromatography and recrystallisation from methanol of (i) yielded a further crop of lanostadienetrione (0·5 g.), $[\alpha]_D$ −51·4° (*c*, 1·80), $\lambda_{max.}$ 211—214 and 286 mμ (log ε 3·99), mixed m. p. not depressed (Found: C, 79·5; H, 9·7%).

Action of Alkaline Hydrogen Peroxide on Lanostadienetrione.—To a solution of lanostadienetrione (100 mg.) in dioxan (10 ml.) was added 10% aqueous potassium hydroxide (2 ml.). The mixture was warmed to 50° and treated with " Perhydrol " (1·5 ml.) for 15 minutes, the colour of the solution becoming pale. Then a further 0·5 ml. of " Perhydrol " was added and after 10 min. the product was poured into water and extracted with ether. The ethereal layer was further extracted with potassium hydroxide solution (10%), then washed with water, and the solvent removed, to leave a negligible neutral fraction. The alkaline fraction was then acidified and extracted with ether. The ethereal solution was washed with water and evaporation of the dried (Na_2SO_4) solvent and crystallisation from ethyl acetate (3 ml.) gave cubic crystals (60 mg.) of the *keto-dicarboxylic acid*, m. p. 229—230° (decomp.), $[\alpha]_D$ −67·0° (*c*, 1·20), $\lambda_{max.}$ 248 mμ, log ε 4·1 (Found : C, 74·0; H, 9·4. $C_{30}H_{46}O_5$ requires C, 74·1; H, 9·5%).

Action of Selenium Dioxide on Lanostanedione.—Lanostanedione (200 mg.) in acetic acid (30 ml.) was heated under reflux for 3·5 hr. with a solution of selenium dioxide (200 mg.) in water (1 ml.). The precipitated selenium was filtered off and the product worked up in the usual way, to give a dark red oil which was adsorbed on alumina (6 × 1·5 cm.) from light petroleum. Elution with light petroleum–benzene (6 : 2) (80 ml.) and recrystallisation from methanol gave plates of *lanost-6-ene-8 : 11-dione*, m. p. 128°, $[\alpha]_D$ +10° ± 5° (*c*, 1·28), $\lambda_{max.}$ 239 mμ, log ε 4·05 (Found : C, 81·6; H, 10·9. $C_{30}H_{48}O_2$ requires C, 81·8. H, 10·9%).

Diketolanostane mono-2 : 4-dinitrophenylhydrazone, obtained by refluxing the reactants for 25 minutes, had m. p. 190°, $\lambda_{max.}$ 371, ε 17,000 (Found : N, 8·8; $C_{36}H_{54}O_5N_4$ requires N, 9·0%).

8-Acetoxylanostan-11-ol.—A solution of lanostanedione (700 mg.) in ether (50 ml.) was added dropwise to a suspension of lithium aluminium hydride (1·2 g.) in ether (100 ml.) with mechanical stirring, under reflux. Stirring was continued for a further 4 hr. and the excess of lithium aluminium hydride was then decomposed by ice-water, followed by dilute sulphuric acid. The mixture was extracted with ether and removal of the solvent gave a gel. Treatment of this with acetic anhydride (20 ml.) and pyridine (5 ml.) on the steam-bath (1 hr.) gave a solid, which after four recrystallisations from acetone–methanol, was *8-acetoxylanostan-11-ol*, needles, m. p. 196—197°, $[\alpha]_D$ +75° (*c*, 0·2) (Found : C, 78·8; H, 11·6. $C_{32}H_{56}O_3$ requires C, 78·6; H, 11·6%).

Dehydration of 8-Acetoxylanostan-11-ol.—8-Acetoxylanostan-11-ol (100 mg.) in pyridine (10 ml.) was treated with phosphorus oxychloride (2 ml.) on a steam-bath for 1·5 hr., then set aside at room temperature for 20 hr. and worked up in the usual way to give a solid, which on recrystallisation from methanol, gave *lanost-10-en-8-yl acetate* (80 mg.), m. p. 139—140°, $[\alpha]_D$ +80·0° (*c*, 1·02) (Found : C, 81·4; H, 11·5. $C_{32}H_{54}O_2$ requires C, 81·6; H, 11·6%). This gave a yellow colour with tetranitromethane.

Modified Wolff–Kishner Reduction of Lanostanedione.—Lanostanedione (900 mg.) in diethylene glycol (20 ml.) was heated under reflux with hydrazine hydrate (0·3 ml., 100%) for 1 hr. at 200°. The mixture was cooled, a solution of sodium (1·0 g.) in diethylene glycol (10 ml.) was added, and the mixture heated under reflux for a further 5 hr. at 230°. The cool solution was diluted with water, acidified, and extracted with ether. The ethereal solution was washed with water and dried (Na_2SO_4). The solvent was removed and the resulting product adsorbed on alumina (6 × 1·5 cm.) from light petroleum. Elution with light petroleum (70 ml.) and crystallisation from chloroform–methanol gave plates (300 mg.) of *lanostan-11-one*, m. p. 94—95°, $[\alpha]_D$ +70° (*c*, 3·04) (Found : C, 84·2; H, 12·2. $C_{30}H_{52}O$ requires C, 84·0; H, 12·2%). The product gave no colour with tetranitromethane.

CHELSEA POLYTECHNIC, MANRESA ROAD, S.W.3.

[*Received, September 19th*, 1952.]

62. *Oenanthotoxin and Cicutoxin. Isolation and Structures.*

By E. F. L. J. Anet, B. Lythgoe, M. H. Silk, and S. Trippett.

Oenanthotoxin, the toxic principle of *Oenanthe crocata*, has been isolated pure and assigned the formula $C_{17}H_{22}O_2$. It is accompanied in the plant by the closely related oenanthetol, $C_{17}H_{22}O$, and oenanthetone, $C_{17}H_{20}O$.

Cicutoxin, the toxic principle of *Cicuta virosa*, has been isolated pure and crystalline for the first time. It is isomeric with oenanthotoxin, and is accompanied in the plant by cicutol, $C_{17}H_{22}O$.

Spectroscopic and degradative evidence defines oenanthotoxin as an all-*trans*-heptadeca-2 : 8 : 10-triene-4 : 6-diyne-1 : 14-diol, and cicutoxin as an all-*trans*-heptadeca-8 : 10 : 12-triene-4 : 6-diyne-1 : 14-diol; the configuration at $C_{(14)}$ in cicutoxin is opposite to that in oenanthotoxin. With a high degree of probability oenanthetol is 14-deoxyoenanthotoxin, oenanthetone is the 14-ketone from 1-deoxyoenanthotoxin, and cicutol is 14-deoxycicutoxin.

Some of the novel features presented by these compounds are mentioned.

The poisonous character of *Oenanthe crocata* (hemlock water dropwort) and *Cicuta virosa* (cowbane; water hemlock) (Umbelliferae) has been known for many centuries; they are said to have been used for both medicinal and criminal purposes. The most poisonous parts of *Oenanthe crocata*, the roots, resemble a bunch of small white carrots, giving the plant the name "five-finger death"; when a root is broken drops of a pale yellow oil appear and rapidly become brown in the air. This oil, which contains the toxin, is easily extracted with ether. The plant is responsible for much poisoning of stock (Fenton and Robertson, *Bull. Edinb. Coll. Agric.*, 1931, **4**, 13, 42) and cases of poisoning among humans, especially children, are common (Pohl, *Arch. exp. Path. Pharmak.*, 1894, **34**, 265; *Lancet*, 1947, II, 485; 1952, I, 155, 316). The water hemlock, *Cicuta virosa* (for description and illustration see Bull. U.S. Dept. Agric., 1913, No. 69), although indigenous to, is less common in, England than *Oenanthe*, but it has caused numerous fatalities in Europe and the United States amongst humans and animals. The rhizome, a bulbous structure with characteristic air-cells, weighs up to 1 kg. and contains a yellow oil similar to that of *Oenanthe*.

Oenanthotoxin and cicutoxin, the poisonous principles, have a very similar pharmocological action, causing violent convulsions and death. They have long been regarded as closely related to each other and possibly also to the picrotoxin group. They were recognised as neutral, non-nitrogenous compounds, but until recently little progress was made in their chemical investigation since neither could be obtained pure or crystalline. Pohl (*loc. cit.*) examined and compared them, and gave crude oenanthotoxin the formula $C_{17}H_{22}O_5$; his crude cicutoxin preparations were somewhat richer in carbon. Jacobson (*J. Amer. Chem. Soc.*, 1915, **37**, 916) gave crude cicutoxin the formula $C_{19}H_{26}O_3$; it resinified in air, reacted vigorously with bromine, and gave oxalic acid on oxidation. Jacobson suggested a structure for cicutoxin containing a *cyclo*pentane and dihydropyrone ring, but it was founded on unsatisfactorily characterised starting material and degradation products and has rightly never been accepted.

In 1949 Clarke, Kidder, and Robertson (*J. Pharm. Pharmacol.*, **1**, 377) purified oenanthotoxin chromatographically and isolated it as colourless crystals, m. p. 80—81°, which decomposed in air to a brown resin. They gave its formula as $C_{18}H_{22}O_4$. Following conversations with Mr. W. D. Robertson, who participated in the above work, we undertook a study of the chemistry of oenanthotoxin. We realised at an early stage that it was a highly unsaturated compound, and the assumption of related properties in cicutoxin then suggested a convenient way for isolating the latter pure. Our studies were consequently widened to embrace both toxins which, as expected, are indeed closely related. Our experiments with them are conveniently described together.

Isolation.—The amounts of oenanthotoxin and ether-soluble contaminants in *Oenanthe crocata* vary seasonally and the method of isolation is best varied accordingly. Fresh roots collected in November or December were used in our first experiments, and these provide

the best starting material. The ethereal extract was purified by shaking it with sodium hydroxide solution, and the product, when treated with carbon tetrachloride, gave crude crystalline material which was readily purified by recrystallisation. The compound so obtained had m. p. 87° and the formula $C_{17}H_{22}O_2$. These values diverge somewhat from those of Clarke and his collaborators, but we confirm their results on the toxicity and instability of the compound and consider their substance was essentially the same as, although a little less pure than, ours. Their incorrect formula was probably largely due to aerial oxidation of their specimen before analysis.

This simple method of isolation failed when applied to the ether-soluble material obtained from fresh roots gathered in April, so the crude oil was analysed chromatographically as described in the Experimental section. A small amount of oenanthotoxin was then obtained, and two other closely related compounds were also isolated pure; these are also present in the autumn plant, but escaped detection in the simple procedure first employed. The first was an alcohol, oenanthetol, $C_{17}H_{22}O$; the second, present only in very small quantity, a ketone, oenanthetone, $C_{17}H_{20}O$. Like oenanthotoxin, both were unstable towards air, and all three compounds had the same very characteristic ultra-violet absorption spectrum (Fig. 1 and Table 3), except for minor differences in intensity.

The nature of this spectrum, together with the realisation that the properties of cicutoxin preparations found by the early workers were consistent with the presence of conjugated unsaturated centres, suggested that cicutoxin too would show long wave-length absorption bands, the intensity of which might be used to control a purification procedure. This view was confirmed when extracts of *Cicuta virosa* were found to show intense and characteristic absorption between 300 and 350 mμ.

The substances responsible for this light absorption were sought by using Brockmann and Volpers' excellent method for the chromatography of colourless substances on aluminium oxide dyed with morin (*Chem. Ber.*, 1947, **80**, 77). Columns of this adsorbent fluoresce when illuminated with ultra-violet light of *ca.* 360 mμ, and those zones which contain material having marked light absorption in the near ultra-violet region then show up as dark bands on a luminous background. In this way, two distinct ultra-violet light absorbing substances were separated from the crude oily extract of *Cicuta* and were purified extensively. The less strongly adsorbed crystallised readily but its complete purification was tedious and wasteful. It furnished a colourless or very faintly yellow alcohol, cicutol, $C_{17}H_{22}O$. The more strongly adsorbed substance was obtained crystalline only with great difficulty; seed crystals were essential for success on subsequent occasions, but if these were available its purification was easier than that of cicutol. The pure material, $C_{17}H_{22}O_2$, isomeric with oenanthotoxin, had essentially the same ultra-violet absorption spectrum as cicutol (Fig. 1; see also Table 3). The name cicutoxin is retained for it, since it had the characteristic convulsant action on mice; cicutol, like oenanthetol, was relatively non-toxic.

All these five compounds formed colourless low-melting crystals which were transformed in air and light into brown insoluble resins. They could be stored unchanged for some weeks below 0° under oxygen-free nitrogen in the dark, and survived recrystallisation from warm solvents and brief heat-treatment during chemical manipulations provided air and light were excluded. Some of their properties are summarised in Table 1.

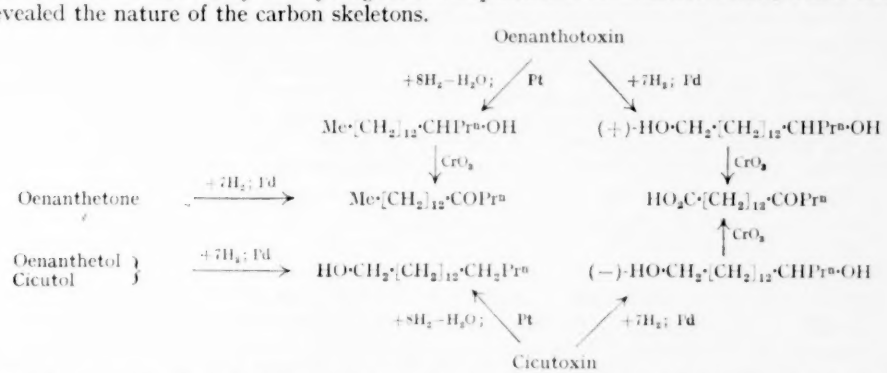
TABLE 1.

	Formula	Toxicity *	M. p.	$[\alpha]_D$
Oenanthotoxin	$C_{17}H_{22}O_2$	+	87°	+30·5° (in MeOH)
Oenanthetol	$C_{17}H_{22}O$	—	71	0 ,,
Oenanthetone	$C_{17}H_{20}O$		46	
Cicutoxin	$C_{17}H_{22}O_2$	+	54	−14·5 (in EtOH)
Cicutol	$C_{17}H_{22}O$	—	66	0 ,,

* 0·2 Mg. suspended in lecithin saline administered intraperitoneally to a mouse of *ca.* 20 g.

Carbon Skeletons and Oxygen Functions.—Oenanthotoxin and cicutoxin are diols, oenanthetol and cicutol alcohols, and oenanthetone is an unconjugated ketone. The oxygen functions were disclosed by the usual reagents but the products were very difficult

to crystallise, and only one derivative, cicutyl acetate, could be obtained crystalline and pure. The natures of the oxygen functions were first indicated by infra-red spectroscopic evidence. All compounds except oenanthetone showed strong bands near 3300 cm.$^{-1}$; the two toxins showed no bands indicative of oxygen functions other than hydroxyl groups, and their very strong adsorption on aluminium oxide suggested that both contained two such groups. Oenanthetone showed a very strong absorption band at 1704 cm.$^{-1}$. This evidence was confirmed by the hydrogenation experiments summarised below, which also revealed the nature of the carbon skeletons.



With palladium in alcohol oenanthotoxin absorbed 7 mols. of hydrogen, giving a saturated aliphatic diol, $C_{17}H_{34}(OH)_2$, which formed a di-1-naphthylurethane. With platinum in alcohol about 7·5 mols. of hydrogen were absorbed, giving a mixture of about equal amounts of the same saturated diol and a saturated alcohol, $C_{17}H_{35}$·OH. Chromic acid oxidised the alcohol to a ketone, $C_{17}H_{34}O$, which was degraded by the Schmidt method with hydrazoic and sulphuric acids in chloroform. After the resulting amide mixture had been hydrolysed, tridecane-1-carboxylic acid, *n*-propylamine, and *n*-tridecylamine were isolated. The saturated alcohol must thus be a heptadecan-4-ol and the ketone must be heptadecan-4-one, and this was confirmed by synthesising the latter from myristoyl chloride and di-*n*-propylcadmium.

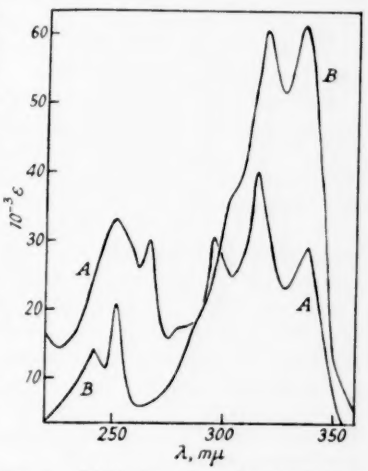


FIG. 1. *Light absorption of oenanthotoxin (A) and cicutol (B) in alcohol.*

Similar methods identified the saturated diol as a heptadecane-1 : 14-diol. On oxidation it gave a keto-acid, $C_{17}H_{32}O_3$, which must be 13-ketohexadecane-1-carboxylic acid, since Schmidt degradation with 1 mol. of hydrazoic acid converted it into an amide mixture which yielded on hydrolysis dodecane-1 : 12-dicarboxylic acid, *n*-propylamine, 12-aminododecane-1-carboxylic acid, and *n*-butyric acid. Since both the alcohol and the diol formed in the hydrogenation with platinum have a hydroxyl group at the same position it is clear that the alcohol was formed by a hydrogenolysis of a primary hydroxyl group at $C_{(1)}$ in oenanthotoxin before saturation. This position must therefore be adjacent to part of the unsaturated system of the toxin.

In the presence of palladium oenanthetol absorbed 7 mols. of hydrogen and gave heptadecan-1-ol, identified by oxidation to hexadecan-1-carboxylic acid. Oenanthetone similarly absorbed 7 mols. of hydrogen and gave the heptadecan-4-one already mentioned. Since all three compounds from *Oenanthe* had the same ultra-violet absorption it is thus probable that oenanthetol is 14-deoxyoenanthotoxin and that oenanthetone is the 14-ketone from 1-deoxyoenanthotoxin.

In methanol with palladium or platinum catalysts cicutoxin absorbed 7 mols. of hydrogen and gave a saturated diol $C_{17}H_{34}(OH)_2$, the enantiamorph of that obtained from oenanthotoxin. Both gave the same 13-ketohexadecane-1-carboxylic acid on oxidation; each had the same m. p. (71°) *, which was depressed on admixture with the other, and neither showed optical activity large enough for detection. The heptadecane-1 : 14-diol from the dextrorotatory oenanthotoxin is here denoted by the prefix *d*-, and that from the lævorotatory cicutoxin by the prefix *l*-, solely for convenience in reference. In acetic acid containing a trace of hydrochloric acid and large amounts of platinum, cicutoxin absorbed nearly 8 mols. of hydrogen; only a small amount of *l*-heptadecane-1 : 14-diol was then formed, the major product being heptadecan-1-ol (m. p. 54°) *. It follows that in cicutoxin $C_{(14)}$, which carries the hydroxyl group eliminated in the above hydrogenolysis, must be immediately adjacent to part of the unsaturated systen.

With a palladium catalyst cicutol took up 7 mols. of hydrogen and formed heptadecan-1-ol; it is therefore probable that cicutol is 14-deoxycicutoxin.

The Chromophores.—The evidence already presented shows that the two unsaturated systems under examination are not of a simple polyene type. If the two toxins contained 7 ethylene links, 6 of them must be conjugated between $C_{(2)}$ and $C_{(13)}$ and both compounds would then have the same ultra-violet absorption as dimethyltetradecahexaene, Me·[CH:CH]$_6$·Me, which absorbs at longer wave-lengths than either (Kuhn, *Angew. Chem.*, 1939, **50**, 703). Infra-red spectroscopic evidence showed that we were dealing with mixed chromophores composed of disubstituted acetylene links and *trans*-ethylene links of the type RCH:CHR'. All five compounds showed bands at about 2200 (RC≡CR' stretching), 2120 (the identity of this band is considered below), 1640 and 1600 (conjugated C=C stretching), and 990 cm.$^{-1}$. The last band is due to the out-of-plane C–H vibrations of the *trans*-RCH:CHR' groups; the normal value for this mode is about 965 cm.$^{-1}$, and the shift to higher frequencies here observed is undoubtedly due to the effect of considerable conjugation. Absorption bands characteristic of allene systems or of *cis*-RCH=CHR' groups were absent. The compounds contained no terminal ethynyl groups since they failed to give silver derivatives.

Both chromophores contain two acetylenic links. This was shown, with oenanthotoxin and cicutol as representatives of each, by partial hydrogenation in the presence of Lindlar's catalyst (*Helv. Chim. Acta*, 1952, **35**, 446), which is selective even for acetylene links which form part of a conjugated system. Figs. 2 and 3 show the changes, similar for both compounds, in the ultra-violet absorption of the two compounds after uptake of 1, 2, and 3 mols. of hydrogen. After 2 mols. of hydrogen had been absorbed the short-wave-length bands had disappeared; the long-wave-length band system had been replaced by a second system, which was typically polyene in type, and both more intense and of a longer wave-length than the original system. The transition to this kind of absorption was incomplete when only 1 mol. of hydrogen had been absorbed. When 3 mols. had been absorbed the intensity of the polyene band system had decreased considerably; the onset of this decrease was apparent when only 2·3 mols. of hydrogen had been absorbed. These changes indicate an initial semi-hydrogenation of two acetylenic links to form two (probably *cis*-)ethylenic links, followed later by a slow general reduction of the whole unsaturated system.

Attempts to isolate the two products of semi-hydrogenation failed, owing to polymerisation. Their light-absorption maxima (Table 2) were very similar, though not identical owing to the different positions of the *cis*-links. Although comparison with the spectra of other unbranched polyenes is complicated by the lack of uniformity in the solvents for which measurements are available, the deviations so caused are unlikely to be large, and it is clear from Table 2 that the products from oenanthotoxin and cicutol both contain a conjugated pentaene system.

* In 1945 M. Sutter and E. Schlittler had extracted *Cicuta virosa* and purified the toxic material extensively; they noticed that the active oily fractions contained highly unsaturated compounds. By hydrogenation of such active extracts they had obtained two crystalline compounds, m. p. 54° and 70°, respectively, but no conclusions could be drawn whether these were derivatives of the physiologically active compounds or not (personal communication from Professor Schlittler).

It follows that both the chromophores under examination contain two acetylene and three ethylene links in conjugation. In both of them too the acetylene links were shown to be adjacent; that is, to form a conjugated diacetylene group. Reaction of oenantho-

TABLE 2. *Light absorption of unbranched conjugated polyenes (wave-lengths in* mμ).

	$\lambda_{max.}$	$10^{-3}\varepsilon$	$\lambda_{max.}$	$10^{-3}\varepsilon$	$\lambda_{max.}$	$10^{-3}\varepsilon$	$\lambda_{max.}$	$10^{-3}\varepsilon$
Me·[CH=CH]$_4$·Me [a]	272	18	282	36	296	52	320	52
Me·[CH=CH]$_6$·Me [b]	328	25	340	46	360	69	375	50
Me·[CH=CH]$_5$·Me [c]	302	—	312	—	330	—	349	—
Pentaene from oenanthotoxin [d]	300	27	315	39	326	47	343	39
Pentaene from cicutol [d]	302	23	315	44	330	63	347	56

[a] In hexane (Kuhn, *loc. cit.*). [b] In chloroform (*idem, ibid.*). [c] Approx., calc. by interpolation. [d] Measured on the alcoholic solutions obtained by semi-hydrogenation.

toxin with methyl iodide and silver oxide gave the dimethyl ether, which did not crystallise, but was readily separated chromatographically from unchanged and partially

FIG. 2.

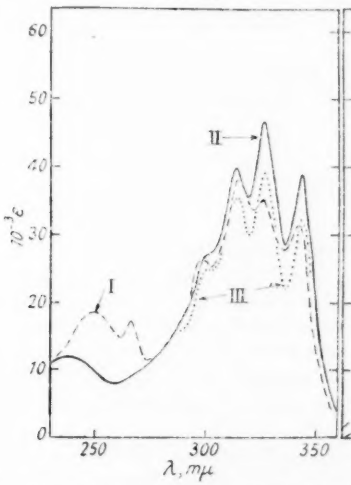


FIG. 3.

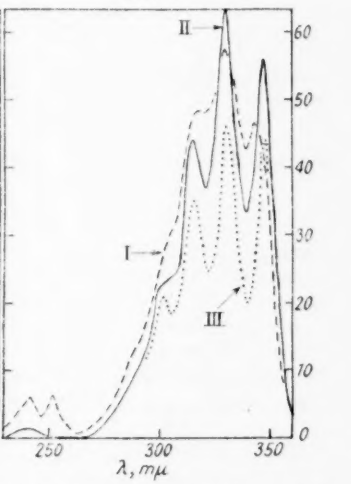


FIG. 2. *Effect of partial hydrogenation on the light absorption of oenanthotoxin in alcohol. After absorption of* (I) 1 *mol.*, (II) 2 *mols., and* (III) 3 *mols. of* H_2.

FIG. 3. *Effect of partial hydrogenation on the light absorption of cicutol in alcohol. After absorption of* (I) 1 *mol.*, (II) 2 *mols., and* (III) 3 *mols. of* H_2.

methylated material, and then showed ultra-violet absorption almost identical with that of the parent compound. When heated with an excess of maleic anhydride the dimethyl ether reacted completely to form an adduct, as shown by the total disappearance of the intense long wave-length absorption bands characteristic of the toxin and the dimethyl ether. Removal of the excess of maleic anhydride was readily effected by partition methods, giving the adduct pure and crystalline. Its ultra-violet absorption maxima were almost identical with those of the dec-2-ene-4 : 6-diyn-1-ol (I) obtained synthetically by Bruun, Haug, and Sörensen (*Acta Chem. Scand.*, 1950, **4**, 850) (see Table 3). The adduct must therefore contain a conjugated ene-diyne system, and have been formed by normal addition of the anhydride to a conjugated diene system situated terminally in the original chromophore.

Cicutoxin gave exactly similar results. The maleic anhydride adduct of its dimethyl ether did not crystallise, but was obtained essentially pure by partition methods; its freedom from unchanged cicutoxin dimethyl ether was shown by the absence of light absorption at 335·5 mμ where the dimethyl ether absorbs very intensely. The ultra-violet absorption maxima of the adduct (Table 3) showed that it contained a conjugated ene-

diyne system and that it must have been formed by normal addition to a conjugated diene system situated terminally in the original chromophore. It follows that one of the two chromophores is that of an ene-diyne-diene (II) and the other that of a triene-diyne (III).

$$\underset{\text{(I)}}{Pr^{n}\cdot[C{\equiv}C]_2\cdot CH{=}CH\cdot CH_2\cdot OH} \qquad \underset{\text{(II)}}{R\cdot CH{=}CH\cdot[C{\equiv}C]_2\cdot[CH{=}CH]_2\cdot R'} \qquad \underset{\text{(III)}}{R\cdot[C{\equiv}C]_2\cdot[CH{=}CH]_3\cdot R'}$$

Heilbron, Jones, and their collaborators have compared the ultra-violet absorption spectra of polyenynes of the types $R\cdot[CH{:}CH]_n\cdot C{:}CH$ and $R\cdot[CH{:}CH]_n\cdot C{:}C\cdot[CH{:}CH]_n\cdot R$ with those of polyenes with the same number of unsaturated centres (*J.*, 1943, 261, 268; 1944, 134, 136). Their results show that the acetylene link causes a diminution in intensity

TABLE 3. *Light absorption in alcohol* (*wave-lengths* in mμ).

	$\lambda_{max.}$	$10^{-3}\varepsilon$		$\lambda_{max.}$	$10^{-3}\varepsilon$
Oenanthotoxin	213	17·5	Cicutoxin	242	13
	252	33		252	22
	267	29		287 *	17
	281 *	17·5		303 *	38·5
	296	30·5		318·5	63·5
	315·5	40		335·5	65
	337·5	29			
Maleic anhydride adduct of oenanthotoxin Me_2 ether	241	8·7	Maleic anhydride adduct of cicutoxin Me_2 ether	241	6·6
	254	16·0		254	13·7
	268	23·0		269	18·9
	284	17·9		284	15·4
Dec-2-ene-4 : 6-diyn-1-ol (I)	239·5	7·3			
	252	14·6			
	266·5	21·8			
	282·5	19·4			

* Inflexion.

and a shift towards shorter wave-lengths of the main absorption band; the reduction in intensity is greater when the acetylenic link is centrally disposed than when it is terminal in the chromophore. If, as seems probable, the effect of a conjugated diyne system is similar, then the light absorption data indicate that the compounds from *Oenanthe* have the ene-diyne-diene chromophore (II) and those from *Cicuta* the triene-diyne chromophore (III), since the latter show long wave-length absorption of very high intensity. These conclusions were confirmed by syntheses of compounds containing the chromophores (II) and (III).

The methods chosen were suggested by the conjugated poly-yne syntheses described by Bohlmann (*Chem. Ber.*, 1951, **84**, 545, 785) and by Jones (Tilden Lecture, *J.*, 1950, 754; for recent fuller accounts of the extensive work of Jones and his co-workers, see *Nature*, 1951, **168**, 900; *J.*, 1952, 1993—2014). In the first of our syntheses, penta-2 : 4-diyn-1-ol, obtained by interaction of formaldehyde and monosodiodiacetylene (Bohlmann, *loc. cit.*) was converted into its dimagnesium bromide derivative (IV) and condensed with octatrienal

$$\text{(IV)}\quad Br\cdot Mg\cdot O\cdot CH_2\cdot[C{\equiv}C]_2\cdot MgBr + OHC\cdot[CH{=}CH]_3\cdot Me$$

$$\downarrow$$

$$HO\cdot CH_2\cdot[C{\equiv}C]_2\cdot CH(OH)\cdot[CH{=}CH]_3\cdot Me \quad \text{(V)}$$

$$\downarrow$$

$$HO\cdot CH_2\cdot[C{\equiv}C]_2\cdot[CH{=}CH]_3\cdot CHMe\cdot OH \quad \text{(VI)}$$

$$\text{(VII)}\quad Me\cdot CH{=}CH\cdot[C{\equiv}C]_2\cdot MgBr + OHC\cdot[CH{=}CH]_2\cdot Me$$

$$\downarrow$$

$$Me\cdot CH{=}CH\cdot[C{\equiv}C]_2\cdot CH(OH)\cdot[CH{=}CH]_2\cdot Me \quad \text{(VIII)}$$

$$\downarrow$$

$$Me\cdot CH{=}CH\cdot[C{\equiv}C]_2\cdot[CH{=}CH]_2\cdot CHMe\cdot OH \quad \text{(IX)}$$

to give the crude diol (V), which when shaken in ether with dilute acid rearranged and furnished the crystalline trideca-6 : 8 : 10-triene-2 : 4-diyne-1 : 12-diol (VI). In the second

synthesis, hept-2-ene-4 : 6-diyne, in the form of its magnesium bromide (VII), was condensed with sorbaldehyde to give the crude alcohol (VIII) from which, after rearrangement in aqueous acidic methanol, crystalline trideca-3 : 5 : 11-triene-7 : 9-diyn-2-ol (IX) was obtained, together with some of its methyl ether.

The ultra-violet absorption spectrum of the triene-diyne (VI) was almost identical with that of cicutoxin (see Fig. 5), confirming that they have the same chromophore; similarly the ene-diyne-diene (IX) and oenanthotoxin had almost identical extinction curves (Fig. 4). The infra-red absorption spectra of the synthetic compounds showed the expected features; in particular they showed a very strong band near 990 cm.$^{-1}$ but none near 690 cm.$^{-1}$, showing that, like the natural compounds, their ethylenic links were all-*trans*.

The structures of the two unsaturated systems being known, two minor points require mention. The presence of a conjugated diacetylene system probably explains the presence of a weak band near 2120 cm.$^{-1}$ in the infra-red spectra of all five natural compounds.

FIG. 4. FIG. 5.

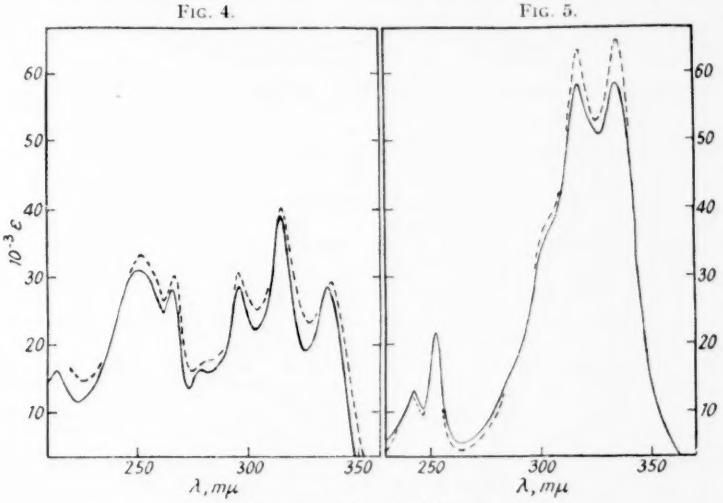


FIG. 4. *Light absorption of*
——— *Trideca-3 : 5 : 11-triene-7 : 9-diyn-2-ol.* – – – – *Oenanthotoxin.* (*Both in alcohol.*)

FIG. 5. *Light absorption of*
——— *Trideca-6 : 8 : 10-triene-2 : 4-diyn-1 : 12-ol.* – – – – *Cicutoxin.* (*Both in alcohol.*)

Dimethyldiacetylene shows bands at 2264 and 2157 cm.$^{-1}$ which are due respectively to the symmetrical and unsymmetrical stretching modes of the acetylene links (see Sheppard and Simpson, *Quart. Reviews*, 1952, **6**, 1), so the band near 2120 cm.$^{-1}$ may well represent the unsymmetrical stretching mode of the diacetylene system. The second point concerns the spacing of the long-wave-length ultra-violet absorption bands in the ene-diyne-dienes (*ca.* 2100 cm.$^{-1}$) and in the triene-diynes (*ca.* 1600 cm.$^{-1}$). In chromophores containing conjugated di- and poly-acetylene links the relevant spacings frequently correspond to the stretching frequency of the acetylene links, a fact which may facilitate the identification of such chromophores in natural products (Bruun, Haug, and Sörensen, *loc. cit.*; Jones *et al.*, *Nature*, 1951, **168**, 900; Anchel, *J. Amer. Chem. Soc.*, 1952, **74**, 1588). The spacing observed in oenanthotoxin fits well into this generalisation, but that observed in cicutoxin corresponds to the stretching frequency of the ethylene, not the acetylene links. It is to be expected that as the proportion of ethylene to acetylene links in a mixed chromophore increases such behaviour will become more prominent, especially where the acetylene links are terminal in the chromophore; in such cases, too, the intensity of the long-wave-length absorption corresponds more closely to that characteristic of purely ethenoid systems.

Position and Orientation of the Chromophores.—In oenanthotoxin and oenanthetol the unsaturated system extends from $C_{(2)}$ to $C_{(11)}$ inclusive; for the toxin this was shown by the

hydrogenolysis of the hydroxyl group at $C_{(1)}$ in the presence of platinum, and for oenanthetol by the isolation of *n*-heptoic acid after complete oxidation with potassium permanganate. In cicutoxin and cicutol the unsaturation extends from $C_{(1)}$ to $C_{(13)}$ inclusive; for the toxin this was shown by the platinum hydrogenolysis of the hydroxyl group at $C_{(14)}$, and for cicutol by the isolation of *n*-valeric and succinic acids after complete oxidation with permanganate. Both unsaturated systems being unsymmetrical, they could be oriented in their respective molecules in two ways, so that oenanthotoxin might be (X; R = OH) or (XI) and cicutoxin might be (XII; R = OH) or (XIII).

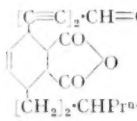
Two methods were used in attempts to decide between these alternatives. If the hydroxyl group at $C_{(1)}$ in oenanthotoxin could be oxidised to the aldehyde or acid stage, a new chromophore would be created which could be identified spectroscopically with the aid of synthetic models. Such oxidations, however, could be effected neither with chromic acid nor with manganese dioxide in non-polar media; both reagents caused more extensive oxidation, and no trace of the desired oxidation products could be found in spite of the sensitive methods available for their detection. An alternative approach, based on the maleic anhydride adducts mentioned earlier, was more successful.

$HO{\cdot}CH_2{\cdot}CH{=}CH{\cdot}[C{\equiv}C]_2{\cdot}[CH{=}CH]_2{\cdot}[CH_2]_2{\cdot}CHRPr^n$ (X)

$HO{\cdot}CH_2{\cdot}[CH_2]_2{\cdot}[C{\equiv}C]_2{\cdot}[CH{=}CH]_3{\cdot}CHRPr^n$ (XII)

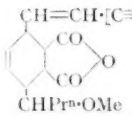
$HO{\cdot}CH_2{\cdot}[CH{=}CH]_2{\cdot}[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}[CH_2]_2{\cdot}CHPr^n{\cdot}OH$ (XI)

$HO{\cdot}CH_2{\cdot}[CH_2]_2{\cdot}[CH{=}CH]_3{\cdot}[C{\equiv}C]_2{\cdot}CHPr^n{\cdot}OH$ (XIII)

(X; R = OH) →  → $MeO{\cdot}CH_2{\cdot}CO_2H$

$[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}CH_2{\cdot}OMe$

$[CH_2]_2{\cdot}CHPr^n{\cdot}OMe$ (XIV)

(XII; R = OH) →  → $MeO{\cdot}[CH_2]_3{\cdot}CO_2H$

$CH{=}CH{\cdot}[C{\equiv}C]_2{\cdot}[CH_2]_2{\cdot}CH_2{\cdot}OMe$

$CHPr^n{\cdot}OMe$ (XV)

Permanganate oxidation of the crystalline adduct from oenanthotoxin dimethyl ether gave a monobasic acid fraction which, when chromatographed on paper (Long, Quayle, and Stedman, *J.*, 1951, 2197), ran as a single spot, identical in position with that given by methoxyacetic acid. This acid was also isolated from the fraction as its benzylamine salt. Its formation as the sole monobasic acid in the oxidation requires the adduct to have the structure (XIV), and oenanthotoxin to correspond to (X; R = OH); a substance of structure (XI) would have formed an adduct which would have given on oxidation γ-methoxy-*n*-heptoic acid, not methoxyacetic acid.

Similar oxidation of the syrupy but carefully purified adduct from cicutoxin dimethyl ether gave as the sole monobasic acid γ-methoxy-*n*-butyric acid, as shown by paper chromatography and also by the isolation of its crystalline piperazine salt; α-methoxy-*n*-valeric acid, which would have been formed instead if cicutoxin had the structure (XIII) was shown to be absent. It follows that the adduct has the structure (XV) and cicutoxin the structure (XII; R = OH).

The orientations of the chromophores in oenanthetol and cicutol have not been directly determined, but it appears almost certain that they are the same as those in the respective diols, leading to the structure (X; R = H) for oenanthetol and to (XII; R = H) for cicutol. It is of interest that in all these compounds the diacetylene system has the same position in the molecule.

The compounds from *Oenanthe* and *Cicuta* belong to the rapidly growing class of naturally occurring poly-ynes, recently investigated representatives of which include matricaria ester (XVI) and dehydromatricaria ester (Holman and Sörensen, *Acta Chem. Scand.*, 1950, **4**, 416; Stavholt and Sörensen, *ibid.*, pp. 1567, 1575), mycomycin (XVII) (Celmer and Solomons, *J. Amer. Chem. Soc.*, 1952, **74**, 1870), and the antibiotics of as yet

undetermined structures which occur in representatives of the Basidiomycetes (Anchel, *loc. cit.*). The present compounds are the first alcohols of the group, and other features of interest include the very uncommon *n*-heptadecane skeletons, the toxicity of the diols, and its virtual disappearance in the mono-ols.

(XVI) $Me{\cdot}CH{=}CH{\cdot}[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}CO_2Me$ $H{\cdot}[C{\equiv}C]_2{\cdot}CH{=}C{=}CH{\cdot}[CH{=}CH]_2{\cdot}CH_2{\cdot}CO_2H$ (XVII)

A summary of some of the above work has already appeared (*Chem. and Ind.*, 1952, **31**, 757). Experiments on the synthesis of the natural compounds and their analogues are in progress.

Experimental

Whenever possible, operations with unsaturated compounds were conducted in diffuse light under oxygen-free nitrogen; evaporations were carried out below 36°, under reduced pressure when necessary. Solvents were carefully purified before use; light petroleum refers to the fraction of b. p. 40—60°, except where otherwise specified. Morin–aluminium oxide refers to material of activity grade II, prepared by Brockmann and Volpers' method (*loc. cit.*).

Isolation of Oenanthotoxin.—Fresh roots of *Oenanthe crocata* (8 kg.), collected in December, were minced and extracted (Soxhlet) with ether (7 l.) for 12 hours. After it had been separated from accompanying water and sludge, the ethereal extract was concentrated to 150 c.c. and shaken with 20% sodium hydroxide solution, which precipitated much colloidal matter. The precipitate was removed and washed with ether, and the combined ethereal solutions shaken with more sodium hydroxide solution, then washed with saturated sodium sulphate solution, dried, and evaporated. The residual oil (10 g.) was dissolved in a small amount of benzene, and warm carbon tetrachloride (35 c.c.) was added, followed by enough light petroleum (b. p. 60—80°) to render the solution just turbid. After 2 days at 0° the crude yellow crystals (3 g.), m. p. 77—80°, were collected and recrystallised successively from benzene, chloroform–light petroleum, methanol, and finally ether, giving *oenanthotoxin* as large prisms, m. p. 87°, $[\alpha]_D^{15}$ + 30·5° (*c*, 2·0 in MeOH) [Found: C, 78·9; H, 8·8%; *M* (ebullioscopic in $CHCl_3$), 245, 275. $C_{17}H_{22}O_2$ requires C, 79·1; H, 8·6%; *M*, 258]. Light absorption: see Fig. 1 and Table 3. The infra-red spectrum showed, *inter al.*, bands at 3390 and 3268 (strong), 2193 and 2123 (v. weak), 1639 (medium), 1590 (weak), and 986 cm.$^{-1}$ (v. strong).

Isolation of Oenanthetol and Oenanthetone.—Fresh roots of *Oenanthe* (7 kg.), collected in March—April, were treated as before, but no crystalline material could be obtained. The combined ether-soluble material (100 g.) from 36 kg. of roots was dissolved in benzene (80 c.c.), the solution shaken with light petroleum (400 c.c.), and the oily precipitate removed and shaken with more light petroleum. The insoluble fraction was extracted with carbon tetrachloride, giving a soluble fraction 1*c* (12 g.) and an insoluble fraction 1*d* (57 g.). The combined light petroleum extracts were evaporated, and the residue dissolved in pentane (250 c.c.) and cooled to −15°, whereupon a gum (fraction 1*b*; 8·7 g.) separated and was removed. Evaporation of the pentane solution gave fraction 1*a* (21·8 g.).

Fraction 1*a* was chromatographed in light petroleum (100 c.c.) on morin–aluminium oxide (1·3 kg.; deactivated with 65 c.c. of water) and the chromatogram developed with the same solvent (2·5 l.). Ultra-violet light of 360 mμ showed a broad upper band which travelled very slowly and a lower narrow band which travelled rapidly. Development was continued with benzene–light petroleum (1 : 1), and the filtrate corresponding to the lower band was collected and evaporated, giving fraction 2*a* (820 mg.). The column was cut and the part corresponding to the upper band was eluted with methanol, evaporation of which gave fraction 2*b* (7·4 g.). Similar chromatography of fraction 1*c* gave two fractions absorbing ultra-violet light—a more (2*d*; 13 g.) and a less strongly adsorbed fraction (2*c*; 4 g.).

Fractions 1*b*, 2*b*, and 2*c* were combined and chromatographed on morin–aluminium oxide (1·2 kg.; deactivated with 72 c.c. of water), and the chromatogram developed with light petroleum–benzene (4 : 1 ⟶ 1 : 1). After 3·5 l. of solvent had been collected a band absorbing ultra-violet light commenced to emerge into the filtrate, which was collected separately (1·2 l.) till desorption of the band was complete. Evaporation gave a pale yellow oil (5·75 g.). When its solution in light petroleum had been kept at 0° for a few days crude crystalline material had separated; recrystallisation from light petroleum gave *oenanthetol* (1·1 g.), m. p. 71° (Found: C, 84·4; H, 9·5. $C_{17}H_{22}O$ requires C, 84·3; H, 9·2%). Light absorption in EtOH: max. at 213, 252, 267, 281, 297, 316, and 338 mμ; $10^{-3}\varepsilon$, 17·5, 30·8, 28·0, 17·0, 28·4, 37·6, and 27·1. The

infra-red spectrum showed *inter al.* bands at 3257 (medium strong), 2193 (v. weak), 2114 (v. weak), 1631 (medium strong), 1587 (weak), and 985 cm.$^{-1}$ (v. strong).

Fraction 2*a* was chromatographed on morin–aluminium oxide (90 g.; deactivated with 6 c.c. of water), and the chromatogram developed with light petroleum. The filtrate corresponding to the broad, fast-moving band was collected separately and evaporated, giving an oil which crystallised when cooled. Recrystallisation from pentane gave *oenanthetone* (50 mg.) as plates, m. p. 46° (Found : C, 85·1; H, 8·3. $C_{17}H_{20}O$ requires C, 85·0; H, 8·4%). Light absorption in EtOH : max. at 251, 267, 280, 296, 315, and 337 mμ; 10^{-3} ε, 30·0, 25·9, 15·0, 27·0, 37·0, and 27·0. The infra-red spectrum showed *inter al.* bands at 2188 (v. weak), 2120 (v. weak), 1704 (v. strong), 1629 (medium), 1582 (v. weak), and 986 cm.$^{-1}$ (v. strong).

By chromatography of fractions 1*d* and 2*d*, oils absorbing ultra-violet light were obtained which on cooling deposited small quantities of crystals, recrystallisation of which gave oenanthotoxin.

Isolation of Cicutoxin and Cicutol.—Fresh rhizomes of *Cicuta virosa* (17 kg.; collected in February) were minced and extracted (Soxhlet) in portions (*ca.* 6 kg.) with ether (8 l.) for 16 hours. After separation from water and sludge the combined extracts were dried and evaporated, and the residue was dissolved in benzene (500 c.c.) and filtered through Hyflo Supercel silica. Evaporation gave a dark brown oil (120 g.) with a terpene-like odour. A portion (15 g.) was chromatographed in benzene (50 c.c.) on morin–aluminium oxide (600 g.), and the column washed with methanol–benzene (1 : 100); when *ca.* 2·5 l. of filtrate had been collected, examination in ultra-violet light revealed three dark zones. The top one was stationary close to the top of the column, the central moved slowly, and the lowest moved rapidly. The filtrate (1 l.) corresponding to the latter was collected separately and evaporated, giving a brown oil (fraction 1; 5·0 g.) which partly solidified at room temperature. After a further 500 c.c. of filtrate had been collected, the next dark band commenced to emerge; the filtrate (2·5 l.) was then collected separately and evaporated, giving a brown gum (fraction 2; 2·5 g.). Elution of the upper zone with methanol and evaporation gave a very dark and dirty gum without the selective light absorption characteristic of the other two zones; it was discarded.

Fraction 1 was adsorbed from benzene (50 c.c.) on morin–aluminium oxide (200 g.), and the chromatogram developed with methanol–benzene (1 : 100). In ultra-violet light a single broad dark zone was seen; in visible light this zone was made up of three parts; leading and trailing edges appeared as narrow brown bands, enclosing a colourless zone. The filtrate corresponding to the last was collected separately; evaporation gave a pale yellow oil (3·4 g.) which solidified completely at room temperature. Crystallisation from light petroleum gave crude material (2·5 g.), m. p. 53—57°. Repeated recrystallisation from benzene–light petroleum and from carbon tetrachloride–light petroleum gave *cicutol* as large, almost colourless plates, m. p. 66°, $[\alpha]_D^{15}$ 0° (*c*, 1·5 in EtOH) (Found : C, 84·4; H, 9·5. $C_{17}H_{22}O$ requires C, 84·3; H, 9·2%). Light absorption in EtOH : max. at 242, 252, 318·5, and 335 mμ : inflections at 287 and 302 mμ; 10^{-3} ε, 14·1, 20·8, 60·6, 61·2, 17·5, and 35·6. The infra-red spectrum showed *inter al.* bands at 3333 (strong), 2212 (medium), 2128 (weak), 1634 (weak), 1603 (medium), and 996 cm.$^{-1}$ (v. strong). With a palladium–charcoal catalyst in alcohol cicutol absorbed 7·2 mols. of hydrogen. Acetylation with pyridine–acetic anhydride at room temperature in the usual manner, and crystallisation of the product from a small volume of light petroleum, gave *cicutyl acetate* as needles, m. p. 38—39·5° (Found : C, 80·0; H, 8·4. $C_{19}H_{24}O_2$ requires C, 80·3; H, 8·4%).

Fraction 2 was adsorbed from benzene (50 c.c.) on morin–aluminium oxide (100 g.), and the chromatogram developed with methanol–benzene (1 : 100). Ultra-violet light revealed a single broad dark zone, the leading edge of which appeared in visible light as a brown band. The filtrate corresponding to the latter was discarded, and that corresponding to the rest of the zone collected separately (*ca.* 2·5 l.) and evaporated. The yellow gum (1·5 g.) so obtained was spectroscopically *ca.* 70% pure; such material could be crystallised directly if seed crystals were available. One such sample crystallised spontaneously at 0° in 5 days, and the crystals were drained from oil and carefully preserved. The following directions are given for the crystallisation, which is not easy. The gum (1·5 g.), dissolved in just enough benzene (*ca.* 20 c.c.) to give a solution clear at 10° but turbid at 7°, was treated at 10° with enough light petroleum to cause marked turbidity, which was removed by addition of ether. The solution was then seeded and kept at 8—9° for 1 hour, whereupon crystallisation usually commenced; if it did not, the operation was repeated with a *larger* volume of solvent. The solution was then cooled progressively to 0° during 6 hours, then kept at 0° for 12 hours, and the dense crystalline deposit (0·9 g.), m. p. 45—49°, collected. Recrystallisation in portions (100 mg.) from ether–light

petroleum gave *cicutoxin* (0·7 g.) as prisms, m. p. 54°, $[\alpha]_D^{15}$ −14·5° (*c*, 1·7 in EtOH) (Found: C, 78·8; H, 8·7. $C_{17}H_{22}O_2$ requires C, 79·1; H, 8·6%). Light absorption: see Fig. 1 and Table 3. The infra-red spectrum showed *inter al.* bands at 3226 (strong), 2212 (weak), 2128 (v. weak), 1634 (v. weak), 1603 (medium), and 996 cm.$^{-1}$ (v. strong).

Hydrogenation of Oenanthotoxin with Palladium.—The toxin (500 mg.) was hydrogenated in alcohol (30 c.c.) with 2·5% palladium–barium sulphate (270 mg.) at room temperature and pressure (uptake, 6·84 mols.). The product, isolated in the usual way, was chromatographed on aluminium oxide and crystallised from chloroform–light petroleum, giving d-*heptadecane*-1 : 14-*diol* (430 mg.) as needles, m. p. 71°, $[\alpha]_D^{12}$ 0° ± 1° (*c*, 2·0 in MeOH) (Found: C, 75·3; H, 13·3. $C_{17}H_{36}O_2$ requires C, 75·0; H, 13·3%). The *bis*-1-*naphthylurethane* separated from chloroform–light petroleum as needles, m. p. 81—82° (Found: C, 76·7; H, 8·1; N, 4·7. $C_{39}H_{50}O_4N_2$ requires C, 76·7; H, 8·2; N, 4·6%).

Hydrogenation of Oenanthotoxin with Platinum.—The toxin (1 g.) was hydrogenated as above in alcohol (50 c.c.) with Adams' platinum catalyst (60 mg.) (uptake, 7·6 mols.). The product was chromatographed on deactivated aluminium oxide, light petroleum with benzene, and later benzene alone, being used for development. The less strongly adsorbed material, namely, *heptadecan*-4-*ol* (440 mg.), crystallised from methanol as needles, m. p. 53°, $[\alpha]_D^{12}$ 0° ± 1° (*c*, 2·0 in MeOH) (Found: C, 80·1; H, 13·9. $C_{17}H_{36}O$ requires C, 79·7; H, 14·0%). The 1-*naphthylurethane* crystallised from pentane as needles, m. p. 82—83° (Found: C, 79·0; H, 10·3; N, 3·4. $C_{28}H_{43}O_2N$ requires C, 79·0; H, 10·2; N, 3·3%).

Crystallisation of the more strongly adsorbed material from the chromatogram from chloroform–light petroleum gave *d*-heptadecane-1 : 14-diol (535 mg.), m. p. 71°, undepressed on admixture with the material described above.

Oxidation of Heptadecan-4-*ol.*—The alcohol (200 mg.), potassium dichromate (200 mg.), concentrated sulphuric acid (250 mg.), and water (0·9 c.c.) were stirred together at 50° for 20 minutes, cooled, and diluted with water (2 c.c.), and the product isolated with ether in the usual manner. Recrystallisation from methanol gave heptadecan-4-one (140 mg.) as plates, m. p. 41—42°; Oldham and Ubbelohde (*J.*, 1939, 201) give m. p. 41·5°.

Schmidt Degradation of Heptadecan-4-*one.*—To a stirred solution of the ketone (1·8 g.) in chloroform (15 c.c.) containing concentrated sulphuric acid (5 c.c.) a 1·15*N*-solution of hydrazoic acid in chloroform (6·6 c.c.) was added slowly at 0°. Stirring was continued a further 15 minutes, crushed ice and more chloroform were added, and the chloroform layer was washed successively with water, 5% aqueous potassium hydroxide, and finally water, then dried and evaporated. The crystalline mixture of amides (1·5 g.) remaining had m. p. *ca.* 63°. A portion (0·5 g.) and 48% hydrobromic acid (10 c.c.) were boiled under reflux for 24 hours, then diluted and cooled to 0°. Tridecylamine hydrobromide which separated was characterised as *N*-*phenyl*-*N*′-*tridecylthiourea*, m. p. 78° (Found: N, 8·6. $C_{20}H_{34}N_2S$ requires N, 8·4%). The filtrate was extracted with ether and the aqueous phase made alkaline and treated with phenyl *iso*thiocyanate, which gave *N*-phenyl-*N*′-*n*-propylthiourea, m. p. 62°, undepressed on admixture with authentic material prepared from *n*-propylamine. The ethereal extract was extracted with dilute aqueous potassium hydroxide, and the alkaline solution acidified, giving a crystalline precipitate which smelled strongly of *n*-butyric acid. Recrystallisation from acetone gave tridecane-1-carboxylic (myristic) acid, m. p. 54°, undepressed on admixture with authentic material. The anilide had m. p. 84° (Found: N, 4·9. Calc. for $C_{20}H_{33}ON$: N, 4·6%).

Synthesis of Heptadecan-4-*one.*—A solution of *n*-propylmagnesium bromide [from *n*-propyl bromide (4·5 g.), magnesium (0·8 g.) and ether (15 c.c.)] was stirred at 0° for ½ hour with anhydrous cadmium chloride (4 g.), and to the stirred suspension tridecane-1-carboxyl chloride (6·5 g.) in ether (25 c.c.) was added slowly. The mixture was heated under reflux for ½ hour, cooled, and poured on crushed ice and dilute sulphuric acid; the ethereal layer was washed successively with water, dilute aqueous potassium carbonate, and water, dried, and evaporated. Crystallisation of the residue from pentane at −30° and recrystallisation from methanol gave the ketone (40%), m. p. 41—42°, undepressed on admixture with material obtained as described above (Found: C, 80·3; H, 13·7. Calc. for $C_{17}H_{34}O$: C, 80·3; H, 13·5%).

Oxidation of d-*Heptadecane*-1 : 14-*diol.*—A mixture of chromic oxide (150 mg.), water (9 c.c.), and concentrated sulphuric acid (1·2 c.c.) was slowly added to a stirred solution of the diol (200 mg.) in acetone (5 c.c.), and the mixture stirred for ½ hour at room temperature, then diluted with water and extracted with ether. The acidic fraction of the product, isolated in the usual manner, crystallised from light petroleum and was recrystallised from ether–light petroleum, giving 13-*ketohexadecane*-1-*carboxylic acid* (100 mg.) as needles, m. p. 79—80° (Found: C, 71·5; H, 11·6. $C_{17}H_{32}O_3$ requires C, 71·8; H, 11·4%).

Schmidt Degradation of 13-Ketohexadecane-1-carboxylic Acid.—A 1·15N-solution of hydrazoic acid in chloroform (0·66 c.c.) was added slowly at 0° to a stirred solution of the keto-acid (180 mg.) in chloroform (2 c.c.) containing concentrated sulphuric acid (0·5 c.c.). Stirring was continued for a further 15 minutes and then ice (4 g.) and more chloroform were added. The chloroform layer was washed with water, dried, and evaporated and the residue boiled under reflux with 48% hydrobromic acid (2 c.c.) for 24 hours. The cooled hydrolysate was diluted with water (10 c.c.) and kept at 0°. *12-Aminododecane-1-carboxylic acid hydrobromide* separated as needles (Found, in material dried at 60°/1 mm.: C, 50·0; H, 8·9; N, 4·8. $C_{13}H_{28}O_2NBr$ requires C, 50·3; H, 9·1; N, 4·5%). The filtrate was extracted with ether, evaporation of which left a solid contaminated by *n*-butyric acid (smell). Recrystallisation from ethyl acetate gave dodecane-1 : 12-dicarboxylic acid (50 mg.), m. p. 125° (Found: C, 65·2; H, 10·5. Calc. for $C_{14}H_{26}O_4$: C, 65·1; H, 10·2%). The aqueous phase from the ether-extraction was made alkaline and treated with phenyl *iso*thiocyanate, giving *N*-phenyl-*N'*-*n*-propylthiurea, m. p. 63°.

Hydrogenation of Oenanthetol.—Oenanthetol (90 mg.) in alcohol (20 c.c.) was hydrogenated in the presence of 2·5% palladium–barium sulphate (uptake, 6·8 mols.). The product, isolated in the usual manner, crystallised from light petroleum, giving heptadecan-1-ol (70 mg.) as plates m. p. 54°, undepressed on admixture with material obtained by hydrogenating cicutol (Found: C, 79·2; H, 14·1. Calc. for $C_{17}H_{36}O$: C, 79·7; H, 14·0%). Levene, West, and van der Scheer (*J. Biol. Chem.*, 1915, **20**, 524) give m. p. 54°. Oxidation in acetone with chromic and sulphuric acids gave hexadecane-1-carboxylic (margaric) acid, m. p. 61°. Le Sueur (*J.*, 1904, **85**, 827) gives m. p. 60—61°.

Hydrogenation of Oenanthetone.—The ketone (15 mg.) was hydrogenated in alcohol (15 c.c.) with palladium–barium sulphate (uptake, 6·7 mols.). The product crystallised from methanol, giving heptadecan-4-one, m. p. 42°, undepressed on admixture with authentic material.

Hydrogenation of Cicutoxin with Palladium.—Cicutoxin (190 mg.) was hydrogenated in methanol (20 c.c.) at room temperature and pressure with 5% palladium–charcoal (50 mg.). The product, isolated in the usual manner, was recrystallised from light petroleum, giving *l-heptadecane-1 : 14-diol* (123 mg.), m. p. 70—71°, depressed to *ca.* 65° on admixture with the *d*-isomer (Found: C, 75·2; H, 13·6. $C_{17}H_{36}O_2$ requires C, 75·0; H, 13·3%). A chromatographic examination of the mother-liquor furnished more diol (40 mg.), but no monohydroxylic compound was detected.

Oxidation of the *l*-diol as described for the *d*-isomer gave 13-ketohexadecane-1-carboxylic acid, m. p. 80—81°, undepressed on admixture with material obtained from the *d*-isomer.

Hydrogenation of Cicutoxin with Platinum in Acetic Acid.—The toxin (150 mg.) in acetic acid (40 c.c.) containing concentrated hydrochloric acid (0·04 c.c.) and Adams's platinum catalyst (100 mg.) was hydrogenated at room temperature and pressure (uptake, 7·95 mols.). The product, isolated in the usual manner, was extracted with cold light petroleum (3 × 7 c.c.). The insoluble residue crystallised from hot light petroleum, giving *l*-heptadecane-1 : 14-diol (7 mg.) as needles, m. p. 70—71°. Evaporation of the light petroleum extract and crystallisation from light petroleum (3 c.c.) at 0° gave heptadecan-1-ol (110 mg.) as plates m. p. 53—54°, undepressed on admixture with material obtained from the hydrogenation of cicutol.

Hydrogenation of Cicutol.—Cicutol (43 mg.) in alcohol (40 c.c.) was hydrogenated with 5% palladium–charcoal (uptake, 7·2 mols.). The product separated from light petroleum (1 c.c.) at 0° as plates (31 mg.) (heptadecan-1-ol), m. p. 54° (Found: C, 79·6; H, 14·2%). Oxidation with chromic and sulphuric acids in acetone gave hexadecane-1-carboxylic acid, m. p. 61° (Found: C, 75·4; H, 12·5. Calc. for $C_{17}H_{34}O_2$: C, 75·5; H, 12·6%).

Reaction of Oenanthotoxin Dimethyl Ether with Maleic Anhydride.—Oenanthotoxin (620 mg.), methyl iodide (90 c.c.), and silver oxide (6 g.) were heated together under reflux with exclusion of light for 24 hours, and fresh silver oxide (2 × 3 g.) was added after 6 and 12 hours. The mixture was filtered, the residue was washed with benzene, the combined filtrate and washings were evaporated, and the residue was chromatographed in benzene on morin–aluminium oxide. Development with benzene caused a homogeneous zone, dark when viewed in ultra-violet light, to travel rapidly down the column. Evaporation of the corresponding filtrate gave the dimethyl ether as an almost colourless gum (700 mg.) with the following light absorption in EtOH: max. at 252, 267, 296, 316, and 337 mμ; $10^{-3}\varepsilon$, 31·5, 29·0, 29·0, 38·3, and 27·6. The gum was heated with maleic anhydride (850 mg.) at 100° for 2 hours, and the cooled mixture dissolved in the top layer (100 c.c.) formed by shaking light petroleum, benzene, methanol, and water (1 : 1 : 1 : 1). The solution was washed with the bottom layer (2 × 100 c.c.) from the same system, and the combined washings were shaken again with more of the top layer (20 c.c.). The united top layers were evaporated, crystallisation of the residue from ether–light petroleum

giving the *adduct* (680 mg.) as colourless needles, m. p. 88·5—89° (Found: C, 72·0; H, 7·5. $C_{23}H_{28}O_6$ requires C, 71·9; H, 7·2%). Light absorption: see Table 3.

Reaction of Maleic Anhydride with Cicutoxin Dimethyl Ether.—Cicutoxin (340 mg.) was methylated for 4½ hours and the product purified as described for oenanthotoxin. The dimethyl ether formed a colourless gum (342 mg.) with the following light absorption in EtOH: max. at 242, 251, 318, and 336 mμ: $10^{-3}\varepsilon$, 15·6, 21·0, 58·0, and 56·8. It was kept at 100° for 1½ hours with maleic anhydride (468 mg.), and the cooled product partitioned between light petroleum, benzene, methanol, and water (1 : 1 : 1 : 1), as described in the case of oenanthotoxin, in order to remove the excess of maleic anhydride. The adduct (395 mg.) could not be crystallised, but its light absorption at 335·5 mμ showed that it contained $<\frac{1}{2}$% of unchanged cicutoxin dimethyl ether (see also Table 3).

Permanganate Oxidation of Oenanthetol.—Finely powdered potassium permanganate (4·5 g.) was added in portions during 1 hour to a well-stirred solution of oenanthetol (500 mg.) in purified acetone (60 c.c.) at room temperature. Stirring was continued for a further 5 hours at room temperature and then under reflux for 40 minutes, all the permanganate being then reduced. The cooled mixture was filtered and the residue washed, first with ice-water and then with hot water. The combined aqueous filtrates were united with the residue obtained by evaporation of the acetone filtrate, acidified strongly with hydrochloric acid, and extracted with ether (7 × 60 c.c.). After the extract had been washed with water (35 c.c.) it was extracted with saturated aqueous sodium hydrogen carbonate (3 × 25 c.c.). The extract was acidified and the product isolated with ether. It formed a brown gum, which was extracted with cold benzene (2 × 10 c.c.); evaporation of the solvent and distillation of the residue under reduced pressure gave crude *n*-heptoic acid (58 mg.), characterised as the piperazine salt (Pollard, Adelson, and Bain, *J. Amer. Chem. Soc.*, 1934, **56**, 1759), needles (from acetone), m. p. 95°, undepressed on admixture with authentic material of m. p. 95—96° (Found: N, 8·4. Calc. for $C_{18}H_{38}O_4N_2$: N, 8·1%).

Permanganate Oxidation of Cicutol.—Cicutol (660 mg.) in purified acetone (60 c.c.) was oxidised with potassium permanganate (5·8 g.) in the same way as oenanthetol. The monobasic acid fraction, isolated similarly, was identified as *n*-valeric acid (130 mg.) by conversion into the piperazine salt (100 mg.), needles (from acetone), m. p. 109° undepressed on admixture with authentic material (Found: N, 9·8. Calc. for $C_{14}H_{28}O_4N_2$: N, 9·8%). Pollard *et al.* (*loc. cit.*) give m. p. 112·5—113°. The aqueous acidic solution from which the valeric acid had been extracted was evaporated under reduced pressure and the residue dried by distillation with benzene and then extracted with hot ether. Evaporation of the extract left a semi-solid residue which was dissolved in an excess of 0·2N-sulphuric acid and titrated at 60° with 1% aqueous potassium permanganate; oxalic acid is oxidised rapidly, succinic acid only slowly by this treatment. An excess of sodium chloride was added, the solution was evaporated again, and the residue dried by distillation with benzene and extracted with hot ether. Evaporation of the extract gave crude succinic acid (75 mg.) which after recrystallisation from water gave pure material (25 mg.), m. p. 183—184°, undepressed on admixture with authentic material. The piperazine salt had m. p. 205—206° (decomp.) in agreement with the value given by Pollard, Adelson, and Bain (*loc. cit.*).

Oxidation of the Maleic Anhydride Adduct of Oenanthotoxin Dimethyl Ether.—The crystalline adduct (630 mg.) in purified acetone (100 c.c.) was treated with stirring with portions of powdered potassium permanganate (2·43 g.) during 2 hours. The mixture was then stirred at room temperature for a further hour and then under reflux for ½ hour, cooled, and filtered, and the residue washed first with ice-water, then with hot water. The aqueous washings were united with the residue left by evaporation of the acetone filtrate, treated with 2N-sodium hydroxide, and concentrated to 100 c.c. The solution was acidified and extracted continuously with ether for 16 hours, and the acidic fraction of the extract isolated by successive transfer to sodium hydrogen carbonate solution and to ether. It formed a brown oil which was extracted with cold benzene (3 × 10 c.c.); evaporation of the benzene and distillation of the residue under reduced pressure gave a crude monobasic acid fraction (90 mg.). Chromatography on paper with alcohol–water–ammonia (Long, Quayle, and Stedman, *loc. cit.*) gave a single spot, identical in position with that given by authentic methoxyacetic acid. The crude material was purified by chromatography on powdered cellulose, the same solvent system being used; this gave methoxyacetic acid (24 mg.), identified by conversion into the *benzylamine* salt (30 mg.), plates (from ethyl acetate), m. p. 110—111·5°, undepressed on admixture with a specimen of m. p. 112—113° prepared from the authentic acid (Found: N, 7·3. $C_{10}H_{15}O_3N$ requires N, 7·1%).

Oxidation of the Maleic Anhydride Adduct of Cicutoxin Dimethyl Ether.—The adduct (462 mg.)

was oxidised in acetone (100 c.c.) with potassium permanganate (1·78 g.), and the monobasic acid fraction of the product (68 mg.) isolated in the way used for the adduct from oenanthotoxin dimethyl ether. As before, paper chromatography showed a single spot, identical in position with that given by authentic γ-methoxybutyric acid, but different in position from that given by α-methoxy-*n*-valeric acid. After purification on a column of powdered cellulose γ-methoxybutyric acid (30 mg.) was obtained and characterised as the *piperazine* salt, needles (from acetone), m. p. 101°, undepressed on admixture with a sample of m. p. 102—103° prepared from the authentic acid (Found : N, 8·8. $C_{14}H_{30}O_6N_2$ requires N, 8·7%).

Trideca-6 : 8 : 10-*triene*-2 : 4-*diyne*-1 : 12-*diol*.—Crude penta-2 : 4-diyn-1-ol (2 g.; Bohlmann, *loc. cit.*) in dry benzene (40 c.c.) was added slowly to a stirred solution of ethylmagnesium bromide [from magnesium (1·46 g.), ethyl bromide (4·5 c.c.), and ether (50 c.c.)], and the mixture stirred at 30° for 3 hours. A solution of octatrienal (4·3 g.) in benzene (60 c.c.) was then added slowly, and stirring continued at 30° for 3 hours. The cooled mixture was decomposed by saturated aqueous ammonium chloride (50 c.c.), and the organic layer washed with water, dried, and evaporated. The residue, dissolved in ether (50 c.c.) containing a trace of quinol, was shaken with 5% aqueous sulphuric acid (100 c.c.) at room temperature for 16 hours, and the mixture extracted with benzene. The extract was washed with water, dried, and evaporated. The residue was subjected to systematic chromatography on morin–aluminium oxide as described for the isolation of cicutoxin, the purity of the various fractions being determined by measuring their absorption intensity at 318 and 336 mμ. The purest fractions from the second chromatogram weighed 152 and 225 mg. respectively; they were combined and recrystallised from benzene, giving the pure *diol* (60 mg.) as prisms, m. p. 111—113° (decomp.) (Found : C, 77·4; H, 7·2. $C_{13}H_{14}O_2$ requires C, 77·2; H, 6·9%). On hydrogenation in alcohol with palladium–charcoal, 6·8 mols. of hydrogen were absorbed. Light absorption in EtOH : max. at 243, 252·5, 317·5 and 335 mμ; inflections at 285 and 303 mμ; 10^{-3} ε, 13·5, 21·3, 57·9, 58·2, 15·0, and 36·0 (see also Fig. 5).

Trideca-3 : 5 : 11-*triene*-7 : 9-*diyn*-2-*ol*.—By reaction with ethylmagnesium bromide (from 0·55 g. of magnesium), hept-2-ene-4 : 6-diyne (1·6 g.) was converted into its Grignard reagent in ether (30 c.c.). The well-stirred solution was treated slowly at 0° during 1 hour with sorbaldehyde (1·8 g.) in ether (20 c.c.), and the mixture heated under reflux for 15 minutes, cooled to 0°, and decomposed with ice and 10% acetic acid. Evaporation of the washed and dried ethereal layer left a residue which was chromatographed on morin–aluminium oxide which had been deactivated by the addition of 4% of water; benzene–light petroleum were used as the solvent; this removed unchanged sorbaldehyde, and elution with methanol and evaporation of the eluate gave the crude reaction product as an oil (1·6 g.) showing the following absorption max. in EtOH : 230, 240, 254, 275·5, and 288 mμ. It was dissolved in 50% aqueous methanol containing 5% concentrated sulphuric acid and a trace of quinol, and after 20 hours at room temperature the solution was diluted and the product isolated with ether. It was purified by chromatography on morin–aluminium oxide, which was controlled by measuring the light-absorption intensity of the fractions at 315 and 336 mμ. Two fractions showing intense absorption at these wave-lengths were obtained. The less strongly adsorbed fraction crystallised from pentane at −50°, giving 2-*methoxytrideca*-3 : 5 : 11-*triene*-7 : 9-*diyne* (30 mg.) as colourless prisms, m. p. *ca.* 0° (Found : C, 83·7; H, 8·2. $C_{14}H_{16}O$ requires C, 84·0; H, 8·0%). Light absorption in EtOH : max. at 214, 250, 266, 279, 296, 315, and 336 mμ; 10^{-3} ε, 18·3, 31·2, 27·3, 15·8, 27·3, 36·8, and 27·3. With palladium–barium sulphate in alcohol it absorbed 7·1 mols. of hydrogen.

The more strongly adsorbed fraction (200 mg.) was recrystallised from light petroleum, giving *trideca*-3 : 5 : 11-*triene*-7 : 9-*diyn*-2-*ol* (120 mg.) as colourless needles, m. p. 73° (Found : C, 84·2; H, 7·6. $C_{13}H_{14}O$ requires C, 83·9; H, 7·6%). Light absorption in EtOH : max. at 214, 252, 266, 279, 296, 315, and 336 mμ; 10^{-3} ε, 16·2, 30·8, 27·9, 16·3, 28·5, 39·0, and 28·4 (see also Fig. 4). With palladium–barium sulphate in alcohol it absorbed 7·0 mols. of hydrogen.

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63. *The Possible Significance of Fenton's Reaction in Relation to Oxidations effected by Enzyme Systems.*

By D. J. Mackinnon and William A. Waters.

Merz and Waters (*J.*, 1949, S 15) classified organic compounds R·H into two groups according to whether oxidation by Fenton's reagent involved chain or non-chain processes. It is now suggested that the classification depends on the oxidation–reduction potential $E_{(-e)}$ of the radical R· for the change $R\cdot \rightleftharpoons R^+ + e$. Substrates undergoing oxidation by the chain process have $E_{(-e)}$ well below E_0 for $Fe^{2+} \rightleftharpoons Fe^{3+} + e$. It has now been found that these same substrates also give radicals capable of reducing two triaryltetrazolium salts to coloured products.

A correlation with enzyme oxidation is suggested; the chain-reacting substrates appear to be those attacked by dehydrogenases which are linked with the pyridine–nucleotide coenzymes. A revised free-radical theory of enzyme oxidation is put forward. Except for peroxidase action it is suggested that a cyclic one-electron redistribution occurs within an enzyme–coenzyme–substrate complex, no *free* radicals being generated.

In a survey of the types of organic molecules which can be oxidised by Fenton's reagent, Merz and Waters (*J.*, 1949, S 15) showed that both chain and non-chain reactions could occur. They represented chain oxidations by the sequence (3), (4), chain initiation being by reaction (1) and chain termination by reaction (2): non-chain reactions did not involve (4) and chain termination required either (5) or (6).

(1) $Fe^{2+} + HO{-}OH \longrightarrow Fe^{3+} + HO\cdot + OH^-$
(2) $Fe^{2+} + \cdot OH \longrightarrow Fe^{3+} + OH^-$
(3) $R{-}H + \cdot OH \longrightarrow R\cdot + H_2O$
(4) $R\cdot + HO{-}OH \longrightarrow ROH + \cdot OH$
(5) $R\cdot + \cdot OH \longrightarrow ROH$
(6) $2R\cdot \longrightarrow$ Products (dimerisation or disproportionation)

They developed two equations to illustrate the essential differences in stoicheiometry of the chain and non-chain processes, *viz.*:

(A) $\Delta[H_2O_2]/\Delta(R{-}H] = 1 + k_3[Fe^{2+}]/k_5[R{-}H]$
(B) $\Delta[H_2O_2]/\Delta[R{-}H] = 2 + k_3[Fe^{2+}]/k_5[R{-}H]$

which were substantiated by showing that, for all the substrates tested, plots of $\Delta[H_2O_2]/\Delta[R{-}H]$ against [Initial Fe^{2+}]/[Initial R–H] had extrapolated intercepts of either 1 or 2 for the condition $[Fe^{2+}]/[R{-}H] = 0$, provided that ΔFe^{2+} was always much less than [Initial Fe^{2+}]. Later (*J.*, 1949, 2427), they pointed out that $\Delta[H_2O_2]$ and $\Delta[R{-}H]$ had to be computed in *equivalents* (not moles), $\Delta[R{-}H]$ being taken as $(\Delta H_2O_2 - \Delta Fe^{2+})$, to allow for the fact that the oxidising equivalent of R–H is different in reaction (6) according as the radical R· dimerises or disproportionates. This essential feature of the theory has been overlooked by Uri (*Chem. Reviews*, 1952, **50**, 403).

Kolthoff and Medalia (*J. Amer. Chem. Soc.*, 1949, **71**, 3777) and Barb, Baxendale, George, and Hargrave (*Trans. Faraday Soc.*, 1951, **47**, 462) pointed out that the chain-continuing reaction (4) is more probably a composite of (7) followed by (1):

(7) $R\cdot + Fe^{3+} \longrightarrow R^+ + Fe^{2+}$; $R^+ + H_2O \longrightarrow R{-}OH + H^+$

and this is substantiated by the fact that addition of a fluoride, which prevents reduction of Fe^{3+} by (7), alters the stoicheiometry of the chain oxidations. Without prejudice to the possibility that with some substrates (4) may also be possible, we accept this view, since it affords a clear theoretical explanation of the second test proposed by Merz and Waters (*loc. cit.*) for the discrimination between chain and non-chain oxidations, *viz.*, the capability of the chain-propagating radicals to reduce both mercuric ions and molecular iodine. We now suggest that organic free radicals and their related cations and anions constitute pairs of thermodynamically reversible oxidation–reduction systems

$R\cdot \rightleftharpoons R^+ + e$, $E_{(-e)}$; $e + R\cdot \rightleftharpoons (R\cdot)^-$, $E_{(+e)}$

to which two different redox potentials can be assigned. Organic radicals which undergo chain oxidation in Fenton's reaction will be those for which $E_{(-e)}$ is decidedly below that of the Fe^{3+}–Fe^{2+} system (+ 0·74 v at pH 0). The redox potentials of the Hg^{2+}–$\frac{1}{2}Hg_2^{2+}$ and $\frac{1}{2}I_2$–I^- systems are sufficiently close in value to this to lead to the same classification of organic radicals by the tests hitherto used. Oxidation–reduction potentials $E_{(+e)}$ have been measured for free radicals of the triphenylmethyl series (Bent and Keevil, *J. Amer. Chem. Soc.*, 1936, **58**, 1228; Keevil, *ibid.*, 1937, **59**, 2104), but in general electrochemical measurements of this type are not practicable because ensuing association reactions, $R^+ + OH^- \rightleftharpoons R{-}OH$ and $R^- + H^+ \rightleftharpoons R{-}H$, are not sensibly reversible under appropriate experimental conditions.

In attempts to develop this concept of the oxidation–reduction potential of a free radical we have sought other oxidation–reduction systems which might be used in hydrogen peroxide–ferrous salt mixtures to demonstrate the relative reducing powers of different radicals. First, we examined oxidation by the similar system hypochlorous acid–ferrous salt, which generates atomic chlorine by reaction (1′) and initiates oxidations by (3′). However, though reaction (3′) is much less effective than (3), as shown by the great change in k_2/k_3 ratios (see Table), all the substrates which undergo chain oxidation with hydrogen peroxide also undergo chain oxidation with hypochlorous acid, because the same reduction of Fe^{3+} by the free radical (7) is involved in each case. This finding is further experimental evidence for the occurrence of reaction (7).

$$(1')\ ^{*}\ Fe^{2+} + HO{-}Cl \longrightarrow Fe^{3+} + OH^- + {\cdot}Cl$$
$$(3')\qquad Cl{\cdot} + R{-}H \longrightarrow R{\cdot} + H{-}Cl$$

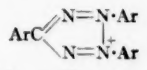
Secondly, we studied the effect of adding dyes to our oxidation mixtures. Unfortunately, compounds such as methylene-blue, sodium indigosulphonate and other dyes regularly used as indicators of reductions effected by titanous chloride, and in biochemical work, do not give unequivocal results. Though they can be reduced reversibly to leuco-compounds they can be oxidised irreversibly by hydroxyl radicals, yielding, sometimes after a sequence of colour changes, colourless or nearly colourless products, and the amount of colour change may be diminished or increased by the addition of an organic substrate in a way which is not always easily explicable (compare Kauffmann, *J. Amer. Chem. Soc.*, 1947, **69**, 899; 1951, **73**, 4311). For instance, methylene-blue is irreversibly bleached by Fenton's reagent but an appreciable amount of hydrogen peroxide is required. If *n*-propanol is added to a methylene-blue–ferrous sulphate solution, and then, *in vacuo*, insufficient hydrogen peroxide to bleach the dye on its own is admixed the colour promptly disappears, but gradually returns slightly. We suggest that the radical $RCH(OH){\cdot}$ reduces the dye to the leuco-base, whilst Fe^{3+}, which is also formed, slowly reoxidises this until an equilibrium is reached. This irreversible oxidation of dyes by the hydroxyl radical has vitiated attempts to use them for quantitative measurement of radiochemical changes in aqueous solution, when both H· and ·OH may be generated simultaneously (compare *Discuss. Faraday Soc.*, 1952, **12**, 133—293). However, we have found that the colourless triaryltetrazolium salts (I), which yield coloured, water-insoluble azo-compounds (II) on reduction, are almost inert to hydrogen peroxide, ferrous sulphate, and their interacting mixture, and yet do give the marked colours of the reduced form (II) when used in the presence of organic substrates, provided that an excess of fluoride is also added so as to form complexes of Fe^{3+} and eliminate competition with reaction (7). The Table shows that two of these salts (*a*) 2 : 3 : 5-triphenyltetrazolium chloride (" red salt "), which gives a red product (II), and (*b*) 3 : 3′-dimethoxydiphenyl-4 : 4′-bis-2″-(3″ : 5″-diphenyltetrazolium) dichloride (" blue salt "), which gives a much more intense blue product, lead to

* Reaction (1′) for the course of electron transfer to hypochlorous acid is to be preferred to the reverse, $Fe^{2+} + HOCl \longrightarrow Fe^{3+} + Cl^- + {\cdot}OH$, since all recent investigators of Fenton's reaction (refs. above) have shown that chloride anions are marked retarders of oxidations by hydroxyl radicals. This has been ascribed to the occurrence of the reaction

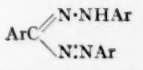
$$HO{\cdot} + H^+ + Cl^- \longrightarrow Cl{\cdot} + H_2O;\quad -F_{298} = 2{\cdot}8 \text{ kcal.}$$

first studied by Taube and Bray (*J. Amer. Chem. Soc.*, 1940, **62**, 3362), which converts active hydroxyl radicals into less active chlorine atoms. Unequivocal chemical evidence for the transient existence of free chlorine atoms in dilute aqueous solution is not yet available.

the classification of oxidisable organic substrates into the same two groups as those listed by Merz and Waters. The radicals of the chain-reaction type are evidently very powerful reducing agents.



(I)



(II)

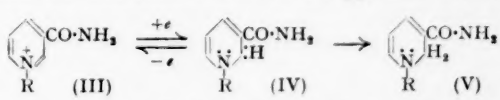
Significance in Relation to Enzyme Oxidation.—Tetrazolium salts (I) can, like methylene-blue, be used in Thunberg's technique for studying dehydrogenase processes (cf. Bertho and Grassmann, "Laboratory Methods of Biochemistry," pp. 152—160, Macmillan, London, 1938) and so it is of interest to examine the listed substrates in relation to their

Classification of free-radical oxidations.

Substrate	Oxidation process: Fe^{2+}–HOCl Intercept	k_3/k_2	Fe^{2+}–H_2O_2 Intercept	k_3/k_2	Effect on tetrazolium salts: * "red"	"blue"
Methanol	1	0·12	1	2·3	+	+
Ethanol	1	0·14	1	3·8	+	+
n-Propanol	1	0·38	1	2·6	+	+
*iso*Propanol	1	0·19	1	3·0	+	+
n-Butanol	1	0·56				
sec.-Butanol	1	0·26				
Diethyl ether	1	0·33	1	6·4		
Tetrahydropyran	1	0·49	1	4·5	+	+
Tetrahydrofuran	1	0·42	1	6·2		
Di*iso*propyl ether	1	0·18			+	+
Ethylene glycol	1	0·21	? 2	3·6	+	+
Butane-1 : 2-diol	1	0·21			—	Slight +
Butane-1 : 3-diol					+	+
Pinacol			2	1·25	—	—
tert.-Butanol	Uncertain		2	0·65	—	—
Methyl acetate	1?		2	0·85	—	Trace +
Ethyl acetate			2	1·10	—	Trace +
Formaldehyde			1	3·0	+	+
Chloral hydrate			2	4·7	—	—
Acetone	No oxidation		No oxidation		—	—
Acetic acid	No oxidation		No oxidation		—	—
Propionic acid			2	0·86		
*iso*Valeric acid			2	3·3	—	—
Succinic acid			—	—	—	—
Adipic acid			2	1·25	—	—
Benzoic acid	Little oxidation		2	7·0	—	—
Maleic acid			No oxidation		—	—
Sodium formate			—	—	+	+
Glycollic acid			1	2·0	+	+
Lactic acid			1	1·7	+	+
Glycine			Uncertain		—	—
Allyl alcohol			—	—	—	—

* See p. 324.

responses to different dehydrogenase enzymes. It can be seen that primary and secondary alcohols, lactic and formic acids, acetaldehyde, and formaldehyde, which are oxidised by the chain reaction, can be biochemically classified together as substrates which undergo biochemical oxidation by enzymes linked to the pyridine-nucleotide coenzymes (Warburg's coenzymes I and II), whereas substrates such as propionic and succinic acids, which are oxidised by the non-chain process, fall into a different biochemical group. Now, it has been established that the biochemical role of the pyridine-nucleotide coenzymes (III)



(III) (IV) (V)

involves their reduction to (V), and it may be noted that the change (III) ⟶ (V), like the change (I) ⟶ (II), is one from an ammonium salt cation to a tertiary amine.

In 1943 (*Trans. Faraday Soc.*, **39**, 140) one of us (W. A. W.) suggested that this reduction

was accomplished by addition of the organic radical to the N^+ centre, but the alternative view that this reduction is like reaction (7), a single-electron transfer (III) $\longrightarrow$ (IV), now seems more probable. We suggest that the biochemically measured oxidation–reduction potentials of the ethanol–acetaldehyde, lactate–pyruvate, and similar systems (cf. Anderson and Plaut in " Respiratory Enzymes," ed. by Lardy, Burgess Pub. Co., Minneapolis, 1949) are in fact the potentials $E_{(-e)}$ for the further oxidation of the substrate radicals $R{\cdot}\dot{C}H{\cdot}OH$ ($\longrightarrow R{\cdot}\overset{+}{C}H{\cdot}OH$). Their values (*ca.* $-0{\cdot}2$ v at pH 7) are comparable with those of Warburg's coenzymes, but well below those of indicator dyes (*e.g.*, methylene-blue $+0{\cdot}01$ v at pH 7) or that for the succinate–fumarate system. When the effects of pH change, and of dissociations of carboxylic acids into their anions, are both taken into account it will be seen that the same structural criteria for radical stability as those discussed by Merz and Waters (*loc. cit.*) in connection with the Fenton reaction apply to substrate–coenzyme relations in dehydrogenase action.

Now, since reaction (III) $\longrightarrow$ (IV) (corresponding to 7) completes the oxidation of the organic substrate, a second one-electron transfer is needed to complete the reduction (IV) $\longrightarrow$ (V) of the coenzyme. This may involve (i) another substrate radical, or (ii) (*in vivo*) the reduced form of another coenzyme, *e.g.*, riboflavin–nucleotide, but (iii) re-oxidation of a metallic ion (8) is also possible, since $E_{(+e)}$ for (IV) may well be high, though $E_{(-e)}$ may be low.

$$(8)\quad H^+ + (IV) + Fe^{2+} \rightleftharpoons (V) + Fe^{3+}$$

Reaction (8) may be compared with the reversible stage of conversion of quinol into benzoquinone by Fe^{3+} (Baxendale, Hardy, and Sutcliffe, *Trans. Faraday. Soc.*, 1951, **47**, 963). In attempting to gauge the values of $E_{(+e)}$ and $E_{(-e)}$ for the semiquinone radicals, analogous to (IV) of indicator dyes, we have reduced methylene-blue and sodium indigodisulphonate, *in vacuo* at pH 7, by the powerful one-electron reduction $[Co(CN)_6]^{4-} \longrightarrow [Co(CN)_6]^{3-} + e$ in the presence of alcohols, and both succinic and maleic acids, but found that addition of each of the organic substrates was without effect. Since under these conditions the reductions of the dyes must occur in two stages, *e.g.*, $MB + H^+ + e \longrightarrow MBH{\cdot}$; $MBH{\cdot} + H^+ + e \longrightarrow MBH_2$, we infer that the forward reactions (9), (10), and (11) do not proceed at rates competitive with the further reduction (12) of the semiquinonoid forms of the dyes, though the reverse processes may well occur easily.

$$(9)\quad MBH{\cdot} + CH_3{\cdot}CH_2{\cdot}OH \longrightarrow MBH_2 + CH_3{\cdot}\dot{C}H{\cdot}OH$$

$$(10)\quad MBH{\cdot} + {}^-O_2C{\cdot}CH_2{\cdot}CH_2{\cdot}CO^- \longrightarrow MBH_2 + {}^-O_2C{\cdot}\dot{C}H{\cdot}CH_2{\cdot}CO_2^-$$

$$(11)\quad MBH{\cdot} + {}^-O_2C{\cdot}CH{:}CH{\cdot}CO_2^- \longrightarrow MB + O_2C{\cdot}\dot{C}H{\cdot}CH_2{\cdot}CO_2^-$$

$$(12)\quad MBH{\cdot} + H^+ + [Co(CN)_6]^{4-} \longrightarrow MBH_2 + [Co(CN)_6]^{3-}$$

Consequently the half-reduced form of the dye cannot be a sufficiently powerful oxidising agent to be capable of abstracting hydrogen very easily from an alcohol, or succinate, molecule, or a sufficiently powerful reducing agent to be able to add hydrogen rapidly to maleate. Initiating reactions, such as (1) and (3) involving hydroxyl radicals and chain-continuing reactions such as (7) and (8) therefore seem to be needed for reduction of a coenzyme (or an equivalent dye) by an oxidisable substrate.

The suggestion that free hydroxyl radicals were involved in dehydrogenase enzyme action was first made by Haber and Willstätter (*Ber.*, 1931, **64**, 2844) : free hydroxyl radicals have been found to oxidise alcohols with great speed and in the requisite manner, but no other chemical oxidisers are known which could operate under the requisite temperature and pH conditions. We therefore suggest that for the enzyme oxidation of the CH·OH group at least stage (i) involves hydroxyl transfer from an enzyme complex by a process equivalent to reactions (1) and (3) of the Fenton scheme, stage (ii) involves the reduction of the coenzyme (III) $\longrightarrow$ (IV) which we have now simulated, and stage (iii) may be represented by reaction (8) in which the reduced centre of the enzyme is re-oxidised to the level requisite for attack on a further substrate molecule. A very similar reaction scheme, in which process (i) is brought about by the photochemical activation of a ferric complex, such as $(FeOH)^{2+}$ or $(FeCl_4)^-$, has been shown by Brealey and Uri (*J.*

Chem. Phys., 1952, **20**, 257) to lead to oxidation of ethanol by thionine (compare Brealey, Evans, and Uri, *Nature*, 1950, **166**, 959; Bates, Evans, and Uri, *ibid.*, p. 869). If, further, one supposes that, before reaction, enzyme and coenzyme form a binary complex, to which the substrate must come up to a specific site to form a ternary complex (Michaelis and Menten, *Biochem. Z.*, 1913, **49**, 333), then the one-electron transfers (i), (ii), and (iii) of the dehydrogenase process can all be represented as occurring within the (enzyme + coenzyme + substrate) complex so that, though organic radicals are concerned, no *free* radicals are involved.

Westheimer, Fisher, Conn, and Vennesland (*J. Amer. Chem. Soc.*, 1951, **73**, 2403), by using 1 : 1-dideuteroethanol, have shown that in the enzyme oxidation of ethanol, hydrogen is transferred directly from the carbinol group to the pyridine–nucleotide co-enzyme. This strongly supports the view that the oxidation occurs by way of a cyclic electron transference within an enzyme–substrate complex from which even a proton cannot escape during the process. The deuterium transfer can easily be represented by writing stage (i) as

$$(\text{Fe–OH})^{2+} + \text{CH}_3\cdot\text{CD}_2\cdot\text{OH} \longrightarrow (\text{Fe,HOD})^{2+} + \text{CH}_3\cdot\dot{\text{C}}\text{D}\cdot\text{OH}$$

and stage (iii) (cf. equation 8) as

$$(\text{Fe,HOD})^{2+} + (\text{IV}) \longrightarrow (\text{IV—D}) + (\text{Fe–OH})^{2+}$$

Here $(\text{Fe–OH})^{2+}$ represents a co-ordinated ferric complex, with hydroxyl as one of the six co-ordinated groups, and $(\text{Fe,HOD})^{2+}$ a ferrous complex with a co-ordinated water (HOD) molecule, following current usage in depicting the corresponding photochemical activation.

Though, to illustrate the analogy with known reactions, we have represented (i) as an electron transference involving a metallic ion of variable valency, we must emphasize that our cyclic oxidation–reduction mechanism is not necessarily restricted to those enzyme systems in which the presence of a transition metal is essential. The initiating agent must have a sufficiently high redox potential to be able to abstract a hydrogen atom from a specific C–H group of the adsorbed substrate, and it is just possible that certain thiyl radicals, R–S·, may be active enough for this purpose (cf. Harris and Waters, *Nature*, 1952, **170**, 212; Bickel and Kooijman, *ibid.*).

A similar cyclic one-electron transfer to the scheme (i), (ii), (iii) was proposed by one of us (Waters, *J.*, 1942, 266) to explain the specific action of cuprous salts in the Sandmeyer reaction, and, as Cowdrey and Davies have pointed out (*J.*, 1949, S 48), it is impossible to show experimentally the actual movements of electrons within a complex in its transition state. Nevertheless, each stage of the process suggested now has an analogous simple chemical reaction that has been observed in the laboratory.

It must be emphasised that the cyclic scheme for dehydrogenase action detailed above refers only to oxidations linked with one or other of Warburg's pyridine–nucleotide co-enzymes, and that the concept that organic radicals have characteristic oxidation–reduction potentials, $E_{(+e)}$ and $E_{(-e)}$, shows why each particular coenzyme system is group-specific. This redox potential concept clearly shows why, *e.g.*, the succinate–fumarate system must be linked to a coenzyme of more positive redox potential, and it may well be that the initiation of this oxidation does not require hydroxyl transfer.

Catalase, however, is another enzyme, almost certainly associated with oxidation by hydroxyl transfer since not only can catalytic decomposition of hydrogen peroxide be brought about by Fe^{3+} and Fe^{2+} ions acting in conjunction, but again catalase does oxidise those same primary and secondary alcohols, etc., which respond to the pyridine–nucleotide linked dehydrogenase. It is easily possible to depict all catalase actions by means of a cyclic electron-transfer process involving ferric ion in the enzyme portion and a molecule of hydrogen peroxide playing the part of coenzyme, and associating with the Fe^{3+} in the type of complex depicted by Chance (*Adv. Enzymology*, 1951, **12**, 153). Whether the electron switches require the possibility of lowering of valency to Fe^{2+}, as suggested in the preceding pages, or of increase in valency to Fe^{4+}, as George's results (*Nature*, 1952, **169**, 612; George and Irvine, *ibid.*, 1951, **168**, 164) may indicate, is again an indeterminable consideration for a transition complex.

Peroxidase, however, though it requires both hydrogen peroxide and an iron-containing enzyme, is evidently quite different in its action from either of the enzymes already mentioned. Its group-specificity is quite distinct, for it does not affect alcohols or aldehydes, but brings about the oxidations of monohydric phenols, aromatic amines, and enediols. As indicated by the work of Cosgrove and Waters (*J.*, 1951, 1726), the products are radical dimers and their degradation products, so that the enzyme must only effect a single-stage one-electron oxidation. This is entirely consistent with George's active ferryl form. Fieser's critical oxidation potential measurements (*J. Amer. Chem. Soc.*, 1930, **52**, 5204) show that the active agent for phenol and amine oxidation must have an oxidation–reduction potential of not less than +1·1 v, and this accords with the postulated existence of a complex containing iron with valency greater than 3.

Experimental

Oxidations with Hypochlorous Acid–Ferrous Sulphate Mixtures.—Hypochlorous acid solutions were prepared by Derbyshire and Waters's method (*J.*, 1951, 75), and the oxidations were carried out as follows: 10 ml. of 0·1N-ferrous ammonium sulphate in 0·5N-sulphuric acid were mixed with the appropriate volume of a standard aqueous solution of the organic substrate and the whole was diluted with distilled water to 40 ml. 10 Ml. of 0·05N-hypochlorous acid were then added with shaking. After 1 hour, or more, the Fe^{3+} content was determined by titration with 0·05N-mercurous perchlorate in the presence of 20 ml. of 10% potassium thiocyanate solution. The titration was carried out in the cold, but the last few drops were added at 60—70° (see Pugh, *J.*, 1945, 588). As in the preceding work by Merz and Waters, freshly boiled-out distilled water was used throughout so as to minimise effects due to free oxygen. Equation (A) was tested graphically for the evaluation of the intercept, and the k_3/k_2 values reported for relative oxidation rates are means of at least six measurements.

Reduction of Tetrazolium Salts.—The two salts, (*a*) 2 : 3 : 5-triphenyltetrazolium chloride ("red salt") and (*b*) 3 : 3′-dimethoxydiphenyl-4 : 4′-bis-2″-(3″ : 5″-diphenyltetrazolium) dichloride ("blue salt") were pure laboratory specimens kindly given to us by Dr. R. Slack. So that the testing should be comparable with our study of Fenton's reaction, all mixtures were made up in 0·1N-sulphuric acid and contained, besides ferrous sulphate solution and an excess of the organic substrate, sodium fluoride solution in amount equivalent to 10 times the Fe^{3+} that might be produced if no oxidation of the substrate occurred. This was usually 5 times the total molar quantity of the ferrous iron. Oxidations were effected by adding sufficient N/200-hydrogen peroxide to oxidise only one-quarter of the ferrous salt. With the "red salt" there was a very slight colour production in the absence of any added organic substrate. The "chain-reacting" radicals all produced a much more intense colour, but some of those of the "non-chain" category produced even less colour than the blank. The "blue salt" produced a much more intense colour with a reactive substrate than did the "red salt," and there was no coloration in the blank. In the absence of fluoride there was no evident reduction of either of the tetrazolium salts to coloured products.

Attempted Induced Reductions with Dye Radicals.—Potassium cobaltocyanide is such a powerful reducing agent that the addition of dilute cobalt sulphate solution to a mixture of an organic dye and potassium cyanide solution brings about immediate reduction of the dye to its leuco-derivative. This great change in the oxidation–reduction potential of cobalt on formation of a complex ion was selected as being a possible model for the activation of a metal-containing enzyme when an enzyme–coenzyme complex is formed.

Thunberg's technique was used. Constant volumes of dye solution, potassium cyanide, and phosphate buffer (pH 7) were mixed in the main Thunberg tube, and after evacuation, dilute cobalt sulphate solution was admixed from the side-tube in amount just sufficient to decolorise the dye. Representative substrates, listed in the Table, were then added to the buffered dye, and tests were made to discover whether any adjustment of the quantity of cobalt salt required for complete decoloration was necessary. Both methylene-blue and sodium indigodisulphonate being used as indicator dyes, all tests gave negative results.

We thank Dr. R. Slack, of Messrs. May and Baker Ltd., for providing us with samples of tetrazolium salts.

The Dyson Perrins Laboratory, Oxford. [*Received, August 9th*, 1952.]

64. *Some Decompositions of Triphenylphenylazomethane in Presence of Quinones.*

By A. J. Betterton and William A. Waters.

The reaction of triphenylphenylazomethane with *p*-benzoquinone to give 2-phenyl-1 : 4-benzoquinone and quinol bistriphenylmethyl ether has been confirmed. 1 : 4-Naphthaquinone gives 2-phenyl-1 : 4-naphthaquinone, but there is no significant attack on phenanthraquinone, chloranil, toluquinone, or 2 : 5-diethoxy-1 : 4-benzoquinone. The reaction may be heterolytic.

Wieland (*Annalen*, 1934, **514**, 157) reported that the decomposition of triphenylphenylazomethane in a benzene solution of *p*-benzoquinone yields quinhydrone, 2-phenylbenzoquinone, and quinol bistriphenylmethyl ether :

$$2Ph\cdot N{:}N\cdot CPh_3 + 5C_6H_4O_2 \longrightarrow Ph_3C\cdot O\cdot C_6H_4\cdot O\cdot CPh_3 + 2Ph\cdot C_6H_3O_2 + (C_6H_4O_2,C_6H_4O_2)$$

In this reaction the active phenyl radical substitutes hydrogen in the quinone nucleus and the displaced hydrogen reduces a portion of the quinone, whilst the less active triphenylmethyl radicals add to the oxygen atoms of the quinone. Nuclear substitution of quinones by free radicals can also be effected by the use of diacyl peroxides (Fieser and Oxford, *J. Amer. Chem. Soc.*, 1942, **64**, 2060; Fieser and Turner, *ibid.*, 1947, **69**, 2338) and may be involved in the reactions between quinones and aromatic diazo-compounds (Kvalnes, *ibid.*, 1934, **56**, 2478). Bickel and Waters (*J.*, 1950, 1764), however, found that the feebly active 2-cyano-2-propyl and 2-carbomethoxy-2-propyl radicals react with *p*-benzoquinone to form only the mono- and di-ethers of quinol. Since different free radicals appear to react in different ways with quinones it was decided to check and extend Wieland's observations.

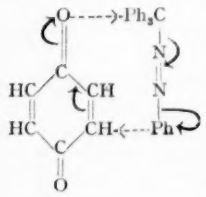
Wieland's reaction yielded a small amount of diphenyl in addition to the substances described by him, indicating that the reaction between phenyl radicals and the solvent described by Hey (*J.*, 1934, 1966) proceeds concurrently with the attack on the quinone. Phenyl ethers of quinol were searched for but could not be detected.

From each of the decompositions, under nitrogen, of benzene solutions of triphenylphenylazomethane in the presence of chloranil, *p*-toluquinone, 2 : 5-diethoxy-1 : 4-benzoquinone, and 9 : 10-phenanthraquinone about 10—15% of the phenyl radicals generated by the azo-compound were recovered as diphenyl; 30—50% of the triphenylmethyl radicals were recovered as triphenylmethyl peroxide, indicating that they had remained largely unchanged until oxygen was admitted in working up the reaction product, for, unlike Hey who performed the decompositions in solution with no other solutes present, we did not continue the heating of our reaction mixture until the destruction of triphenylmethyl was complete. No derivatives of any of these quinones could be isolated; recoveries of unchanged material ranged from 50 to 90% even when the azo-compound was used in excess.

On account of the low solubilities of these quinones in benzene these reactions had to be conducted in dilute solution; this would favour reactions of the free radicals with the solvent, but nevertheless *p*-benzoquinone itself was attacked at a comparable molar concentration. All these quinones are readily attacked, on oxygen, by 2-cyano-2-propyl radicals (Lopez Aparicio and Waters, *J.*, 1952, 4666).

However, the decomposition of triphenylphenylazomethane in a benzene solution of 1 : 4-naphthaquinone does also lead to the formation of a quinhydrone, substantially that of unsubstituted naphthaquinone, and also of some 2-phenyl-1 : 4-naphthaquinone. Triphenylmethane and triphenylmethyl peroxide have also been isolated, but no definite evidence of the formation of a triphenylmethyl ether has been obtained. It may be significant that 1 : 4-naphthaquinone is easily alkylated in the nucleus by diacyl peroxides and that it is the only quinone with which direct nuclear attack by 2-cyano-2-propyl radicals has been observed (Lopez Aparicio and Waters, *loc. cit.*). From our experiments it was noticeable that nuclear phenylation occurs only when a portion of the quinone is

reduced to quinhydrone. This reduction may be an essential feature of the reaction mechanism, and the results would then be consistent with the view that a bimolecular heterolytic reaction between triphenylphenylazomethane and quinone accompanies the unimolecular homolysis of the azo-compound. This leads to nuclear phenylation and cationoid triphenylmethyl attack on oxygen, not necessarily on the same quinone molecule.



The scheme resembles that used for explaining the Thiele acetylation of quinones, and it may be noted that the inactive quinones do not readily undergo this acetylation reaction. An analogous heterolytic decomposition of an unsymmetrical diacyl peroxide has been described by Leffler (*J. Amer. Chem. Soc.*, 1950, **72**, 67). This heterolytic reaction may become evident only when a sufficiently reactive catioenoid system is available to allow the bimolecular process to proceed much more rapidly than the normal homolysis.

Experimental

The decomposition of triphenylphenylazomethane in the presence of *p*-benzoquinone was carried out in benzene solution under nitrogen at 70° as described by Wieland (*loc. cit.*). From 6·3 g. (0·018 mole) of azo-compound, 5·4 g. of benzoquinone (0·05 mole) and 50 c.c. of benzene there were obtained, in three experiments, 0·77, 0·82, and 0·80 g. of quinhydrone, m. p. 110°, and 1·77, 1·85, and 1·83 g. of quinol bistriphenylmethyl ether, m. p. 230—233° (decomp.) (Schmidlin, *Ber.*, 1910, **43**, 1300, gives m. p. 235°; Wieland gives 230°) (Found: C, 88·8; H, 5·5. Calc. for $C_{44}H_{34}O_2$: C, 88·8; H, 5·8%). In a separate experiment the crude product was steam-distilled after the solvent and quinhydrone had been removed. Unchanged benzoquinone (0·86 g.) was recovered, together with an oil (0·22 g.) which was nitrated at 100° with nitric acid–acetic acid, yielding 4-nitrodiphenyl, m. p. and mixed m. p. 110—112°. Attempts to separate other reaction products by chromatographic methods were not successful. In a later experiment half the above quantities of solids were allowed to interact in 250 c.c. of benzene, whereupon in spite of this ten-fold dilution there were obtained 0·37 g. of quinhydrone, 0·04 g. of 2-phenyl-*p*-benzoquinone, and 0·8 g. of the quinol diether.

Decomposition of Triphenylphenylazomethane in Presence of 1 : 4-*Naphthaquinone.*—Freshly prepared 1 : 4-naphthaquinone (4·54 g., 0·029 mole) was dissolved in dry benzene (25 c.c.) and heated to 70° under oxygen-free nitrogen, and a solution of the azo-compound (4·0 g., 0·0115 mole) in benzene was added in small portions during 30 min. so as to minimise radical–radical interactions. The colour of the solution changed from yellow to dark brown as the reaction proceeded and, on cooling, purple-blue crystals (0·3 g.) separated. After being washed with benzene these had m. p. 162° (decomp.) [the quinhydrone of 1 : 4-naphthaquinone has m. p. 175° (decomp.); that of 2-phenylnaphthaquinone has m. p. 136°]. This quinhydrone in ether was shaken with acid aqueous ferric chloride; the ethereal layer on evaporation then gave semi-crystalline material, which after recrystallisation from ethanol gave 1 : 4-naphthaquinone, m. p. and mixed m. p. 124—125°. Another portion was reductively acetylated and yielded colourless needles of 1 : 4-diacetoxynaphthalene, m. p. and mixed m. p. 128—130°.

The filtrate from the quinhydrone was evaporated almost to dryness and the residue was extracted with hot light petroleum (b. p. 60—80°; 70 c.c.). This solution was concentrated to 20 c.c., diluted with an equal volume of ethanol, and set aside, whereupon colourless crystals (0·05 g.) separated. On crystallisation from benzene–light petroleum (1 : 1) these proved to be bistriphenylmethyl peroxide, m. p. and mixed m. p. 186° (decomp.). Identity was confirmed by comparison of its infra-red spectrum with that of an authentic specimen prepared from triphenylmethyl chloride.

The filtrate from the peroxide was treated with twice its volume of ethanol and set aside. Yellow needles (0·32 g.) separated which after crystallisation from ethanol proved to be 2-phenyl-1 : 4-naphthaquinone, m. p. and mixed m. p. 110° (Found: C, 82·1; H, 4·30. Calc. for $C_{16}H_{10}O_2$: C, 82·2; H, 4·3%).

In a second experiment the quinhydrone (0·28 g.) was removed as described above and the solution was then concentrated to 20 c.c. and cooled. A brown solid (0·32 g.) separated, which after crystallisation from ethanol proved to be unchanged naphthaquinone, m. p. and mixed m. p. 124°. The remaining liquid was evaporated to dryness and then distilled in steam, yielding 0·06 g. of triphenylmethane, m. p. and mixed m. p. 92°.

In a third experiment the solution, after removal of the quinhydrone, was diluted with light petroleum (b. p. 60—80°) and passed down an alumina column. The first eluate yielded tetraphenylmethane (0·07 g.), m. p. and mixed m. p. 285°, and then followed triphenylmethane (0·26 g.), m. p. and mixed m. p. 94° (from ethanol). Extraction with benzene–light petroleum (3 : 1) gave 2-phenyl-1 : 4-naphthaquinone, m. p. and mixed m. p. 109° (from ethanol), but subsequent elution gave no pure products.

Decompositions in Presence of Other Quinones.—(*a*) A solution of the azo-compound (6 g.) in benzene (20 c.c.) was added in portions during 30 min. to a solution of chloranil (4·24 g., 1 mol.) in benzene kept at 70° under nitrogen. When gas evolution had ceased, the solution was boiled for 5 min. to complete the reaction. After evaporation of most of the benzene under nitrogen the remaining liquid was extracted with alkaline sodium dithionite solution to remove unchanged chloranil and then concentrated under nitrogen, yielding a mobile gum. Treatment of this with ether separated bistriphenylmethyl peroxide (1·3 g.). After crystallisation from benzene–light petroleum (b. p. 80—100°; 1 : 1) this had m. p. 186° (decomp.) and an infra-red spectrum identical with that of an authentic specimen (Found: C, 87·5; H, 5·8. Calc. for $C_{38}H_{30}O_2$: C, 88·0; H, 5·8%). The remaining gum was steam-distilled and yielded diphenyl (0·3 g.) which was identified as its 4-nitro-derivative, m. p. and mixed m. p. 112°. The total recovery of unchanged chloranil was 90%, and when the quantities of azo-compound and chloranil were changed to 3 g. and 1 g. respectively remained as high as 75%.

(*b*) From a similar reaction of 4 g. of azo-compound with 6 g. of phenanthraquinone in 350 c.c. of benzene, 5·5 g. of quinone were recovered together with 1·0 g. of bistriphenylmethyl peroxide and 0·25 g. of diphenyl.

(*c*) From 0·9 g. of toluquinone and 5 g. (2 mol.) of azo-compound there were recovered 0·44 g. of unchanged quinone, 1·8 g. of peroxide, and 0·25 g. of diphenyl. Chromatographic separation of other products was not successful.

(*d*) From 2·83 g. of 2 : 5-diethoxy-1 : 4-benzoquinone, m. p. 184° (Knoevenagel and Bückel, *Ber.*, 1901, **34**, 3994), and 2 g. of the azo-compound in 60 c.c. of benzene, 1·88 g. (67%) of unchanged quinone were recovered. Chromatography of the remainder led to the isolation of 0·06 g. of triphenylmethane and 0·87 of bistriphenylmethyl peroxide. From another experiment 0·09 g. of diphenyl was recovered by steam-distillation.

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65. *Simple Pyrimidines. Part I. Spectroscopic Studies.*

By D. J. BROWN and L. N. SHORT.

The nature of the potentially tautomeric groups in hydroxy- and amino-pyrimidines has been studied by means of ultra-violet and infra-red spectroscopy. In aqueous solution 4-"hydroxypyrimidine" exists predominantly in the lactam (ketonic) form and the aminopyrimidines in the amino-form. The preparation of hitherto unknown monosubstituted pyrimidines is described.

OUR knowledge of the structure of potentially tautomeric groups in the pyrimidine and related systems has been summarized by Marshall and Walker (*J.*, 1951, 1004). Although the structure of the hydroxy- and mercapto-groups in the simple pyrimidines seems fairly clear from their ultra-violet spectra, there is some uncertainty regarding the amino-pyrimidines.

In order to extend the spectroscopic data, we examined a series of pyrimidines having only one group attached to the nucleus, and that of the simplest type (OMe rather than OEt). The decision to exclude superfluous alkyl groups necessitated the synthesis of a number of new pyrimidines. Such of these as lacked a hydrogen-bonding group (*e.g.*, 2-dimethylaminopyrimidine) were characterized by high volatility, high solubility in the majority of solvents, and marked hygroscopicity.*

* Since this investigation was undertaken, Boarland and McOmie (*J.*, 1952, 3716) have reported the spectra of 2-methoxy-, and 2- and 4-amino-pyrimidine.

Preparations.—For simplicity, the potentially tautomeric compounds will be referred to as "amino-" or "hydroxy-" without prejudice to the final conclusions.

The commercially available 2-aminopyrimidine has been hydrolysed to 2-hydroxypyrimidine (Brown, *Nature*, 1950, **165**, 1010). It was also readily converted by diazotization, etc. (Howard, U.S.P. 2,477,409/1949) into 2-chloropyrimidine, and this yielded 2-methoxy-, 2-methylamino-, and 2-dimethylamino-pyrimidine.

Both 2- and 4-aminopyrimidine were readily acetylated in good yield (cf. Baddiley, Lythgoe, and Todd, *J.*, 1943, 561; Marshall and Walker, *loc. cit.*). Although this does not contribute evidence in favour of the amino-form for these amines, it at least disposes of the supposed difference in behaviour towards acetylating agents between the 2- and 4-isomers on the one hand and the unequivocally *amino*-5-isomer on the other.

Since 4-chloropyrimidine can be obtained only in small yield from 4-hydroxypyrimidine and is unstable (Boarland and McOmie, *J.*, 1951, 1218), it was used as an intermediate in only one case. The crude mixture derived from 4-hydroxypyrimidine and phosphoryl chloride gave with excess of sodium methoxide a poor yield of 4-methoxypyrimidine. It resembled the 2-methoxypyrimidine in general properties but was so readily hydrolysed in weakly acidic aqueous solution that complete potentiometric titration could not be satis-

FIG. 1. FIG. 2.

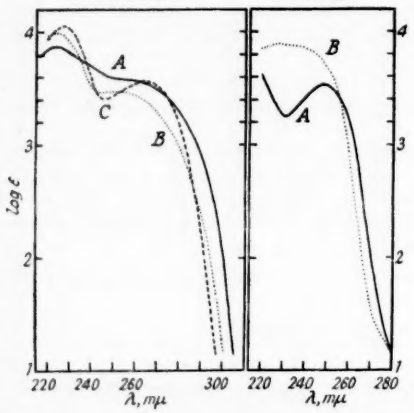


FIG. 1. *4-Hydroxypyrimidine:*
A, *neutral* (pH 6·16).
B, *cation* (pH *approx.*—1; 5N-H_2SO_4).
C, *anion* (pH 13; N/10-KOH).

FIG. 2. *4-Methoxypyrimidine:*
A, *neutral* (pH 6·95).
B, *cation* (pH 0; N-HCl).

factorily performed nor could the ultra-violet spectrum of the cation be recorded with the usual accuracy. In the case of 4-methylaminopyrimidine, the unfavourable direct synthesis from 4-chloropyrimidine and the cumbersome method of Winkelmann (*J. pr. Chem.*, 1927, **115**, 292) were both replaced by a much simpler route. 2 : 4-Dimercaptopyrimidine was converted into 2-mercapto-4-methylaminopyrimidine according to Russell, Elion, Falco, and Hitchings (*J. Amer. Chem. Soc.*, 1949, **71**, 2279). Desulphurization with Raney nickel thence produced 4-methylaminopyrimidine. A related method gave 4-dimethylaminopyrimidine. Although 4-aminopyrimidine was available by a similar synthesis from thiocytosine (Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353), it was decided to explore a new route from 4-amino-5-cyanopyrimidine, available in one step from formamidine and malononitrile (Baddiley, Lythgoe, and Todd, *J.*, 1943, 386). This nitrile was readily converted in good yield into the acid both directly and by way of the amide. Decarboxylation, however, gave only a 25% yield of 4-aminopyrimidine on a small scale, and even this could not be achieved with larger quantities.

Spectroscopy.—In considering the structure of compounds such as the hydroxypyrimidines it is important to note that in solution an equilibrium will exist between the possible tautomeric forms (*e.g.*, I). For the simpler case of 4-hydroxyquinoline Tucker and Irvin (*J. Amer. Chem. Soc.*, 1951, **73**, 1923) have found that the equilibrium constant for the tautomerism (K_T), defined as $K_T = C_K/C_E$ (where C_K and C_E are the concentrations of the ketonic and the enolic form respectively), has the value $1{\cdot}29 \times 10^4$ at 20°, showing that the ketonic (lactam) form predominates. The simple treatment used by the above authors

cannot be applied to the pyrimidines owing to the number of possible structures involving the two ring-nitrogen atoms. For example, use of the pK_a values given by Marshall and Walker (*loc. cit.*) and the method of Tucker and Irvin (*loc. cit.*) leads to a value of 9 for K_T of 4-hydroxy-6-methylpyrimidine, favouring the ketonic form : this seems unreasonably low; however, the ultra-violet spectra of aqueous solutions indicate the keto to be the predominant form.

The spectra obtained for 4-hydroxypyrimidine (anion, cation, and neutral molecule, Fig. 1) and 4-methoxypyrimidine (cation and neutral molecule, Fig. 2) closely resemble those reported by Marshall and Walker (*loc. cit.*) for 4-hydroxy- and 4-methoxy-6-methylpyrimidine respectively. The spectra of the two compounds, however, are so different that the proportion of 4-hydroxypyrimidine existing in the lactim form (I*a*) in aqueous solution must be very small. Boarland and McOmie (*loc. cit.*) compared the spectra of 2-hydroxy- and 2-methoxy-pyrimidine and concluded that the lactam form (II*b*) is strongly favoured in aqueous solution. The conclusions reached by Marshall and Walker (*loc. cit.*)

FIG. 3. FIG. 4.

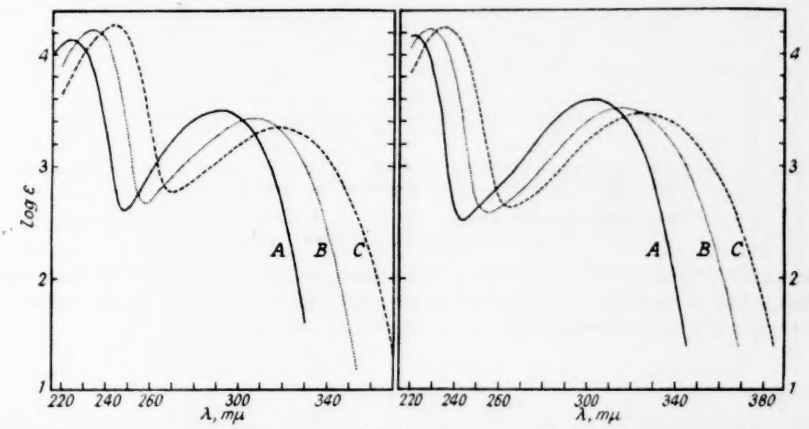
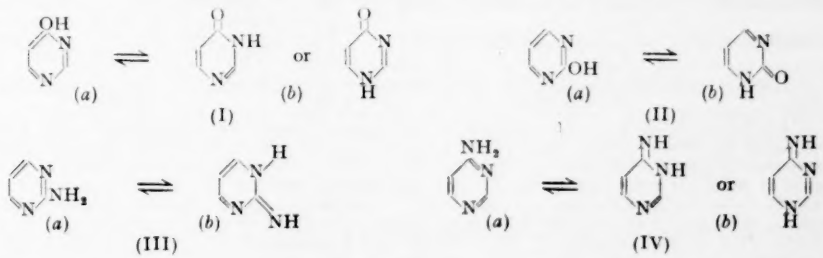


FIG. 3. *A*, 2-*Aminopyrimidine* (*neutral*; pH 7·0). *B*, 2-*Methylaminopyrimidine* (*neutral*; pH 7·0). *C*, 2-*Dimethylaminopyrimidine* (*neutral*; pH 7·0).

FIG. 4. *A*, 2-*Aminopyrimidine* (*cation*; pH 1; N/10-HCl). *B*, 2-*Methylaminopyrimidine* (*cation*; pH 1). *C*, 2-*Dimethylaminopyrimidine* (*cation*; pH 1).

from a study of the monomethylhydroxypyrimidines are thus confirmed, and their claim that the methyl group in such compounds as 2-hydroxy-4-methylpyrimidine makes little difference to the structure and spectral behaviour of the compounds is substantiated.



Considerable uncertainty has existed regarding the tautomerism of 2- and 4-amino-pyrimidine, which may exist in the corresponding iminodihydro-forms (III*b*, IV*b*). The spectra of these compounds and of the corresponding monomethylamino- and dimethyl-amino-pyrimidines are shown in Figs. 3—6. From the method of synthesis, the structures

of the dimethylamino-compounds are unambiguously known. The close similarity between the spectra of the amino-, monomethylamino-, and dimethylamino-compounds provides strong, if not conclusive, evidence that 2- and 4-aminopyrimidine exist chiefly

FIG. 5. FIG. 6.

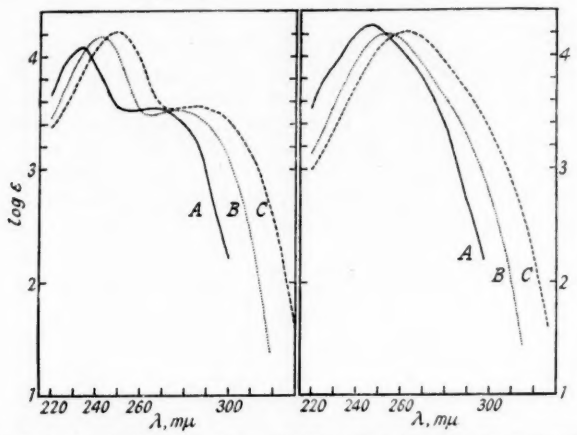


FIG. 5. *A*, 4-*Aminopyrimidine* (*neutral;* pH 13). *B*, 4-*Methylaminopyrimidine* (*neutral;* pH 9·05). *C*, 4-*Dimethylaminopyrimidine* (*neutral*; pH 9·28).

FIG. 6. *A*, 4-*Aminopyrimidine* (*cation;* pH 0). *B*, 4-*Methylaminopyrimidine* (*cation;* pH 2·07). *C*, 4-*Dimethylaminopyrimidine* (*cation;* pH 3·15).

in the amino- (III*a*; IV*a*) rather than the iminodihydro-form (III*b*; IV*b*) in aqueous solution. The substitution of a methyl group for a hydrogen atom of the amino-group produces a small bathochromic shift in the absorption maxima.

Pyrimidine	pK_a[1] (20°)	pH	$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$ *
4-Hydroxy-	1·69 ± 0·04	13	227, 263	4·05, 3·56
	8·60 ± 0·02	6·2	223,[2] 260 †	3·87, 3·57
		−1	224, 251	3·99, 3·47
4-Methoxy-[3]	2·5 ± 0·2	6·95	247—248	3·53
		0	227—228, 238 †	3·89, 3·86
2-Amino	3·54 [4]	7·0	224, 292	4·13, 3·50
		1 [5]	221, 302—303	4·17, 3·60
2-Methylamino-	3·82 ± 0·03 ‡	7·0	234, 306—307	4·23, 4·33
		1	228, 315	4·23, 3·53
2-Dimethylamino-	3·96 ± 0·01	7·0	243, 318	4·26, 3·35
		1	235, 324—325	4·24, 3·47
4-Amino-[6]	5·71 [4]	13	233, 268—269	4·26, 3·72
		0	246	4·27·
4-Methylamino-	6·12 ± 0·04 §	9·0	242, 276—277	4·18, 3·54
		2·1	254	4·20
4-Dimethylamino-	6·35 ± 0·02	9·3	250, 286	4·22, 3·56
		3·15	262	4·21

* ε (molar extinction coefficient) = d/Cl, where d = optical density, C = molar concn., l = cell length. † Inflexion. ‡ 22°. § 23°.

[1] All the pK_a's are for M/100-solution except those of 2-aminopyrimidine (M/10) and 4-aminopyrimidine (M/200). [2] Boarland and McOmie gave $\lambda_{max.}$ 227·5 (log ε 3·97) and Albert, Brown, and Cheeseman (*J.*, 1951, 474) gave $\lambda_{max.}$ 225 (log ε 3·83). The latter result was obtained from measurements at 5-mμ intervals and the maximum was between 220 and 225 mμ. [3] Sensitive to acid. [4] Albert, Goldacre, and Phillips, *J.*, 1948, 2240. [5] Stimson (*J. Amer. Chem. Soc.*, 1949, **71**, 1470) gave $\lambda_{max.}$ 220 (log ε 4·10) and 300 (3·58) at pH 3 when about 20% of the compound would have been present as the neutral molecule. [6] Values taken from Boarland and McOmie (*J.*, 1952, 3716).

Infra-red spectra of some of the compounds discussed above have also been measured. It has been shown (Short and Thompson, *J.*, 1951, 168) that the infra-red spectra of the hydroxypyrimidines in the solid state indicate their ketonic character. The spectra of 2- and 4-methoxypyrimidine have now been measured and are shown along with those of

2- and 4-hydroxypyrimidine in Fig. 7 for the range 1300—1800 cm.$^{-1}$. Each of the hydroxy-compounds has a very strong absorption band in the 1600—1700 cm.$^{-1}$ region which has no counterpart in the spectra of the methoxy-compounds and must be due to carbonyl bond stretching vibrations.

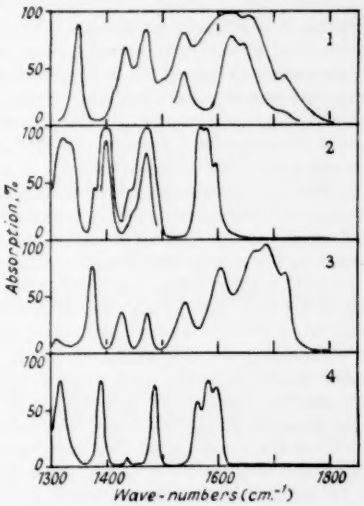


FIG. 7. *Infra-red spectra:*
1, 2-*Hydroxypyrimidine* (*solid*),
2, 2-*methoxypyrimidine* (*liquid*),
3, 4-*hydroxypyrimidine* (*solid*),
4, 4-*methoxypyrimidine* (*liquid*).

The infra-red spectra of 2- and 4-aminopyrimidine in dilute solution in carbon tetrachloride have been measured in the region of N–H bond stretching vibration frequencies. Each compound gives the two strong bands characteristic of the amino-group, proving that these compounds exist in the amino-form in this solvent. These spectra will be discussed in more detail in a later paper.

EXPERIMENTAL

Physical Measurements.—pK_a *Values.* These were determined by potentiometric titration of aqueous solutions of the compound with hydrochloric acid or potassium hydroxide solution. The values determined are shown in the Table.

Ultra-violet spectra. The ultra-violet spectra were measured with a Hilger "Uvispek" Spectrophotometer. The substances were dissolved in suitable buffers (phosphate, glycine) or acid or alkali solution (potassium hydroxide, hydrochloric acid, sulphuric acid) of pH such as to give the desired species (neutral, anion, or cation). The pH was chosen to be at least 2 units greater or less than the relevant pK_a value, thus ensuring at least 99% of the required species.

Infra-red spectra. These were measured with a Perkin–Elmer Model 12C recording spectrometer, a lithium fluoride prism being used for the 3000—3550 cm.$^{-1}$ region and a sodium chloride prism for the 1300—1800 cm.$^{-1}$ region.

Syntheses.—(Analyses were by Mr. P. R. W. Baker, Beckenham. M. p.s are uncorrected.)

2-*Methoxypyrimidine.* Crude 2-chloropyrimidine (2 g.) was added to sodium methoxide (from sodium, 0·5 g., and methanol, 25 ml.), and the solution refluxed for 30 min. After cooling, carbon dioxide was passed in to saturation, the solution was filtered, and the solvent removed in a vacuum. The residual mass was extracted with ether (40 ml.). After drying (K_2CO_3), the ether was removed, and distillation then gave 0·83 g. (43%) of colourless mobile 2-*methoxypyrimidine*, b. p. 70—71°/15 mm., n_D^{20} 1·5060 (Found: C, 54·15; H, 5·5; N, 25·15. $C_5H_6ON_2$ requires C, 54·55; H, 5·5; N, 25·45%).

2-*Dimethylaminopyrimidine.* Crude 2-chloropyrimidine (2·4 g.) and methanolic dimethylamine (15%; 20 ml.) were heated at 120° for 1 hour. Sodium methoxide (from sodium, 0·4 g., in methanol, 20 ml.) was added and the product worked up as above (but with omission of the refluxing); 2-*dimethylaminopyrimidine* (1·2 g., 46%) was obtained as a colourless hygroscopic liquid, b. p. 78—81°/17 mm., n_D^{22} 1·5438 (Found: C, 58·5; H, 7·35; N, 33·8. $C_6H_9N_3$ requires C, 58·45; H, 7·4; N, 34·1%).

2-*Methylaminopyrimidine.* Ethanolic methylamine and 2-chloropyrimidine similarly gave

a 49% yield of distillate, b. p. 91—92°/14 mm., which solidified. Recrystallization from light petroleum (b. p. 60—80°; 10 parts) gave colourless laths of 2-*methylaminopyrimidine* (non-hygroscopic), m. p. 59—61° (Found: C, 55·15; H, 6·45; N, 38·95. $C_5H_7N_3$ requires C, 55·05; H, 6·5; N, 38·5%). Concentration gave a second crop of slightly less pure material.

4-*Methoxypyrimidine*. Phosphoryl chloride (25 ml.) was heated with 4-hydroxypyrimidine (7 g.) under reflux at 125° (bath) for 25 min. The cooled mixture was shaken with light petroleum (b. p. 40—60°; 6 × 15 ml.) which removed most of the phosphoryl chloride. To the residue was added dry methanol (60 ml.). A vigorous reaction ensued, some liquid boiling over. The clear yellow solution was added in a thin stream to sodium methoxide solution (from sodium, 10 g., and methanol, 125 ml.) Salts were precipitated, and the suspension was refluxed on the steam-bath for 30 minutes. After treatment as for the 2-isomer, 4-*methoxypyrimidine* was obtained as a colourless, mobile liquid (2·2 g.), b. p. 69—70°/30 mm., n_D^{20} 1·4980 (Found: C, 54·45; H, 5·45; N, 25·0%). It was hygroscopic and miscible with all solvents.

4-*Dimethylaminopyrimidine*. 2 : 4-Dimercaptopyrimidine (10·2 g.) was heated in a sealed tube with aqueous (or aqueous-alcoholic) dimethylamine (25%; 60 ml.) for 3 hours at 130°. After evaporation, the residue was treated with cold hydrochloric acid (0·5N; 200 ml.) in which most of it dissolved, leaving dimercaptopyrimidine. The filtrate was brought to pH 3—4, thereby precipitating colourless crystalline 4-dimethylamino-2-mercaptopyrimidine (8·25 g.; m. p. 278°, decomp. from 265°). This material was dissolved in boiling water (370 ml.) and treated portionwise with Raney nickel (45 g. wet weight). The suspension was boiled under reflux for 30 minutes and filtered hot, the solid washed with hot water (100 ml.), and the combined green filtrates were treated again with fresh nickel (20 g.) as before. To the now colourless filtrate was added sodium chloride (160 g.), and the solution was continuously extracted with ether for 15 hours. The extract was dried (K_2CO_3), the solvent removed, and the residue distilled at 131—132°/50 mm., to give 3·1 g. (50%) of 4-*dimethylaminopyrimidine*, hygroscopic, m. p. *ca.* 40° (Found, for solid dried for 48 hours over P_2O_5: C, 57·9; H, 7·4; N, 34·2%), readily soluble in all common solvents.

4-*Methylaminopyrimidine*. 2-Mercapto-4-methylaminopyrimidine (12 g.; Russell *et al.*, *loc. cit.*) was treated in boiling water (300 ml.) with Raney nickel (60 + 40 g.) as above. The crude product was distilled from a flask with a very wide side arm in which the product solidified (5 g., 54%). It had b. p. 142—144°/16 mm. and m. p. 69—72° (Winkelmann, *loc. cit.*, gives 74—75°), forming very hygroscopic needles from light petroleum (Found: C, 54·95; H, 6·0; N, 38·2. Calc. for $C_5H_7N_3$: C, 55·05; H, 6·5; N, 38·5%).

2-*Acetamidopyrimidine*. 2-Aminopyrimidine (0·48 g.) and acetic anhydride (1·5 ml.) were heated at 120° (bath) for 1 hour. The red liquid was cooled and deposited a solid. Acetone (5 ml.) was added, the slurry chilled to 0° and filtered, and the cake washed with cold acetone (3 ml.) to give 0·45 g. (56%) of almost white solid, m. p. 145°. Two recrystallizations (the first with charcoal) from *iso*butyl methyl ketone (25 parts) gave large, colourless laths of 2-*acetamidopyrimidine*, m. p. 145—146·5° (Found: C, 52·5; H, 5·1; N, 30·7. $C_6H_7ON_3$ requires C, 52·6; H, 5·15; N, 30·65%). It was readily soluble in cold water, ethanol, or chloroform and in hot carbon tetrachloride, but rather less in hot light petroleum (b. p. 80—100°).

4-*Aminopyrimidine-5-carboxyamide*. Formamidine was condensed with malononitrile according to Baddiley *et al.* (*J.*, 1943, 386), and the resulting 4-amino-5-cyanopyrimidine recrystallized from water (40 parts); it had m. p. 248—251° (decomp.). The cyano-compound (7·4 g.) was added to a stirred mixture of N-potassium hydroxide (55 ml.) and hydrogen peroxide (3%; 225 ml.) in a bath at 50—55°. A crystalline deposit began to form after ½ hour, and after a further ½ hour the pH was adjusted to 7 and the suspension was cooled to 0° for 2 hours (yield, 5·6 g., 66%). Recrystallization from water (35 parts) with charcoal gave a 90% recovery of colourless laths of 4-*aminopyrimidine-5-carboxyamide*, m. p. 254—256° (Found: C, 43·4; H, 4·05; N, 40·45. $C_5H_6ON_4$ requires C, 43·5; H, 4·35; N, 40·55%), readily soluble in dilute acids but not in alkali. It is soluble in 28 parts of boiling water but not readily recrystallized therefrom.

4-*Aminopyrimdine-5-carboxylic acid*. (*a*) From the nitrile. The nitrile (1·9 g.) and sodium hydroxide solution (2·5N; 19 ml.) were heated on the steam-bath for 1 hour with occasional shaking at first. The solution was brought to pH 4 with concentrated hydrochloric acid. After refrigeration, the solid was washed with a little cold water and dried at 130° (2·0 g., 78%; m. p. 270—272°). Recrystallization from water (17 parts; charcoal) gave the acid (1·75 g.), m. p. 278—281° (Found, in material dried at 130°/0·1 mm.: C, 43·1; H, 3·7; N, 29·95. $C_5H_5O_2N_3$ requires C, 43·2; H, 3·6; N, 30·2%). It was readily soluble in dilute acids and alkali and showed only one fluorescent spot on a paper chromatogram.

(*b*) From the amide. 4-Aminopyrimidine-5-carboxyamide (4·25 g.) and 2·5N-sodium hydroxide (40 ml.) were heated on the steam-bath for 30 min.; the acid, worked up as above (3·8 g., 89%), had m. p. 270—274°, and was identical with that produced from the nitrile.

Decarboxylation of 4-aminopyrimidine-5-carboxylic acid. The carboxylic acid (0·5 g.) was added (2 min.) to benzophenone (5 g.) at 280°. Evolution of carbon dioxide ceased after a further 5 min. When the melt had cooled to 100°, light petroleum (b. p. 100—120°; 25 ml.) was added, and after being chilled the solid was filtered off. It was recrystallized from *iso*butyl methyl ketone (50 parts; carbon) to give 0·1 g. of 4-aminopyrimidine, m. p. 150° not depressed by an authentic sample of m. p. 151—152°. Decarboxylation by direct destructive distillation of the carboxylic acid, with collection of the product in the side arm of the flask, gave about the same yield of purified product. Neither method could be improved to give good yields.

4-Acetamidopyrimidine. 4-Aminopyrimidine was acetylated similarly to the 2-isomer (above) in 77% yield. Recrystallized from *iso*butyl methyl ketone (20 parts), *4-acetamidopyrimidine* was obtained as colourless needles, m. p. 198—200° (Found: C, 52·55; H, 5·05; N, 30·65%). Its solubilities were slightly lower than those of the 2-isomer.

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66. *Studies on Fructosans. Part IV.* A Fructosan from* Dactylis glomerata.

By G. O. Aspinall, E. L. Hirst, (the late) E. G. V. Percival, and R. G. J. Telfer.

A fructosan from mid-season leafy cocksfoot grass (*Dactylis glomerata*) gave on hydrolysis D-fructose (97%) and D-glucose (3%). Methylation and hydrolysis yielded 1 : 3 : 4 : 6-tetramethyl D-fructose (4%), 2 : 3 : 4 : 6-tetramethyl D-glucose (1·8%), 1 : 3 : 4-trimethyl D-fructose (93·3%), and a dimethyl D-fructose (0·7%). The greater part of the material possesses therefore a molecular structure comprising a straight chain of *ca.* 25 2 : 6-linked fructofuranose residues terminated by a glucopyranose residue linked as in sucrose.

Fructosans of the levan type have been isolated from various plants such as rough-stalked meadow grass (*Poa trivialis*) (Challinor, Haworth, and Hirst, *J.*, 1934, 1560), barley leaves (Haworth, Hirst, and Lyne, *Biochem. J.*, 1937, **31**, 786), the roots of timothy-grass (*Phleum pratense*) (Schlubach and Sinh, *Annalen*, 1940, **544**, 101), and perennial rye-grass (*Lolium perenne*) (Laidlaw and Reid *). The present investigation has shown the fructosan from mid-season leafy cocksfoot grass (*Dactylis glomerata*) to possess a similar structure. Previous observations by Bell and Palmer (*Biochem. J.*, 1949, **45**, xiv) suggested a repeating unit of 14 residues for this fructosan, although physical measurements of sedimentation and diffusion constants suggested a chain length of 32—33. Palmer (*Biochem. J.*, 1951, **48**, 389), by estimation of the glucose produced on hydrolysis and on the basis of one glucose residue per chain, put forward values of 29 and 37 for the chain lengths of different samples of leafy-cocksfoot levan.

The cocksfoot grass used was oven-dried milled material prepared from grass cut in May, 1949, at the Jealott's Hill Agricultural Research Station. After preliminary extraction with ether and 80% aqueous methanol, the fructosan was extracted from the grass with water. Hydrolysis of the purified polysaccharide and analysis of the product by paper

* Part III, *J.*, 1951, 1830.

chromatography (Hirst and Jones, *J.*, 1949, 1659; Duff and Eastwood, *Nature*, 1950, **165**, 848) showed the presence of fructose (97%) and glucose (3%).

The fructosan was methylated under nitrogen with sodium hydroxide and methyl sulphate, and the product (OMe, 44·6%) was fractionated by dissolution in chloroform–light petroleum. Fraction 3 (OMe, 45·2%) was hydrolysed and the mixture of sugars separated on a cellulose column (Hough, Jones, and Wadman, *J.*, 1949, 2511). Two fractions (A and B) were obtained, corresponding to those previously observed on the paper chromatogram to be tetramethyl fructofuranose (containing some tetramethyl aldose) and a trimethyl fructose. Further elution yielded a small amount of a dimethyl fructose, which travelled at the same rate on the chromatogram as 3 : 4-dimethyl D-fructose. The tetramethyl fructofuranose was shown colorimetrically (cf. Arni and Percival, *J.*, 1951, 1822) to be present to the extent of *ca.* 4% in the hydrolysate. Its identity was confirmed by conversion into the crystalline tetramethyl D-fructofuronamide (Avery, Haworth, and Hirst, *J.*, 1927, 2313). Hypoiodite oxidation showed the presence of *ca.* 15% of tetramethyl aldose in A, and extraction of the remainder of the syrup with light petroleum gave a residual syrup from which some 2 : 3 : 4 : 6-tetramethyl D-glucose crystallised on seeding. Fraction B (93·3%) crystallised completely and proved to be 1 : 3 : 4-trimethyl D-fructose. Hypoiodite oxidation indicated at most only traces of aldose derivatives in this fraction.

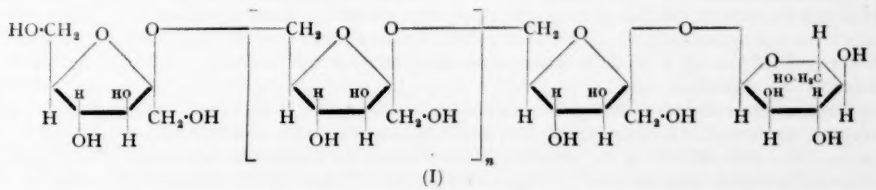
In order to attempt a quantitative separation of tetramethyl glucose a further quantity of methylated fructosan was hydrolysed, and the resulting sugars converted into the corresponding glycosides. Extraction in a liquid-extractor with light petroleum (Brown and Jones, *J.*, 1947, 1344) gave only partial separation of tetramethyl methylfructoside from tetramethyl methylglucoside. Each fraction was hydrolysed and the free sugars were separated on cellulose columns. Complete separation of tetramethyl glucose from tetramethyl fructose was eventually achieved by partition chromatography. The tetramethyl aldose was identified as 2 : 3 : 4 : 6-tetramethyl D-glucopyranose, and the total quantities present in the various fractions were estimated by hypoiodite oxidation. The presence of a trace of trimethyl aldose in the trimethyl fructose fraction was shown both by hypoiodite oxidation and by paper chromatography, but the quantity (*ca.* 1 mg.) was without structural significance. A small quantity of a dimethyl fructose was also obtained from the column but this substance was not present in sufficient amount for complete identification.

From these experiments the proportions of the various methylated sugars produced on the hydrolysis of the methylated fructosan are tetramethyl fructofuranose 4·0%, tetramethyl glucopyranose 1·8%, trimethyl fructofuranose 93·3%, and dimethyl fructose 0·7%. The proportion of tetramethyl fructose indicates a chain of *ca.* 25 fructofuranose units in the fructosan. The quantity of dimethyl fructose is too small to be of structual significance and probably arises from undermethylation of the polysaccharide and/or demethylation during the hydrolysis. The quantity of tetramethyl glucose isolated, although not accounting for all the glucose present, does not permit of one residue per chain but suggests that a large proportion of fructosan molecules are terminated by a non-reducing glucose residue probably present in a sucrose-type linkage. It is possible that some degradation took place during the isolation and methylation of the polysaccharide with scission of some terminal glucose units. The absence of all but traces of other methylated glucoses eliminates the possibility of a contaminating glucosan's being present with the fructosan. Measurement of the molecular weight of the methylated fructosan by Barger's method (cf. Caesar, Gruenhut, and Cushing, *J. Amer. Chem. Soc.*, 1947, **69**, 617) gave a value corresponding to 17—25 $C_9H_{16}O_5$ units.

Oxidation of the polysaccharide consumed *ca.* 1·02 moles of sodium metaperiodate per $C_6H_{10}O_5$ residue, in agreement with the postulate of a molecule composed of fructofuranose residues linked through the 2 : 6-positions. Oxidation with potassium periodate (Brown, Halsall, Hirst, and Jones, *J.*, 1948, 27) yielded 1 mole of formic acid per 19—20 $C_6H_{10}O_5$ residues.

Heating the fructosan in water at 100° caused autohydrolysis. The fall in pH and the change in specific rotation were followed and samples were examined on the chromatograms as the reaction proceeded, spots being obtained corresponding to sucrose, glucose, fructose,

and three unidentified acids. The " autohydrolysis " is at least in part a breakdown of the fructosan by acid hydrolysis.



(I)

These experiments essentially confirm the structure deduced from methylation data and show that this fructosan possesses a structure (I) very similar to that proposed for the fructosan from perennial rye-grass (Laidlaw and Reid, *loc. cit.*). The production of formic acid on periodate oxidation is slightly greater (1 mole per 19—20 $C_6H_{10}O_5$ residues) than would be expected if all the chains are terminated by a glucopyranose residue (1 mole per 25 residues). If, as has been suggested, scission of some of the terminal residues has occurred then the yield of formic acid from a reducing fructofuranose residue would explain the observed increase.

The structure of the fructosan as a chain of fructofuranose units linked through the 2 : 6-positions and terminated by a glucopyranose unit linked as in sucrose is in full agreement with the theories put forward by Dedonder (*Compt. rend.*, 1950, **230**, 549, 997; 1951, **231**, 790; **232**, 1134, 1442) and by Bacon and Edelman (*Biochem. J.*, 1951, **48**, 114; **49**, 446, 529) that fructosans are built up in the plant from sucrose by enzymic trans-fructosidation.

Experimental

Preparation and Properties of the Polysaccharide.—Portions (100 g.) of mid-season cocksfoot grass (oven dried; H_2O, 9·8%; cut, May 26th, 1949) were extracted with ether (1 l.) for 5 hours. The residue was filtered and dried, then extracted with 80% aqueous methanol for a further 5 hours, after which the grass was filtered off and extracted for 3 hours with fresh 80% aqueous methanol (1 l.). The residue was removed, dried in air, and shaken with distilled water (1·3 l.) for 12 hours at room temperature. The grass was removed by filtration and washed with water, and the extract and washings (*ca.* 300 c.c.) were combined. The solution was heated to 93°, cadmium sulphate solution (40 c.c.; 10%) and sodium hydroxide solution (20 c.c.; 0·5N) were added, and the whole was kept at 95° for 3 minutes. After cooling, the cadmium hydroxide–protein complex was removed by filtration through " Filter Cel " (cf. Doak, *N.Z. J. Sci. Tech.*, 1939, **21**, 90B). The clear filtrate was de-ionised on columns of Amberlite resins (I.R.-100 and I.R.-4B), and the last traces of protein were removed by chloroform (0·25 vol.)–butanol (0·1 vol.) (Sevag, Lackmann, and Smollens, *J. Biol. Chem.*, 1938, **124**, 425). Evaporation of the neutral solution to 100 c.c. gave a light-amber coloured solution, which was poured into methanol. The colourless fructosan precipitated was removed at the centrifuge, washed twice with acetone, and dried in a vacuum-desiccator (P_2O_5 and paraffin wax). The polysaccharide was thus obtained as a fine colourless powder. By repetitions 30 g. of fructosan were prepared and combined. The average yield was *ca.* 3% of the dry weight of the grass. The fructosan had $[\alpha]_D^{15}$ −40·4° (*c*, 1·7 in H_2O) (Found: ash, 0·37; as sulphate, 0·45; N, 0·05%), and slowly reduced boiling Fehling's solution.

The fructosan (0·149 g.) was heated in 0·1N-oxalic acid (10 c.c.) at 70°, the following changes being observed: $[\alpha]_D^{15}$ −40·3° (0 min.); −46·3° (10 min.); −67·1° (20 min.); −78·5° (30 min.); −83·9° (40 min., const.). Paper chromatograms run in ethyl acetate–water–acetic acid (4 : 4 : 1 and 6 : 6 : 1) showed the hydrolysate to contain only fructose and a little glucose.

Hydrolysis of the polysaccharide until the rotation became constant ($[\alpha]_D^{15}$ −85° in 0·1N-oxalic acid), followed by neutralisation, filtration, de-ionisation, and concentration, gave a reducing solution which was shown chromatographically to consist of fructose *ca.* 97% and glucose *ca.* 3%. The fructose was estimated by oxidation with sodium metaperiodate as described by Hirst and Jones (*loc. cit.*), and the glucose by the Nelson colorimetric method (Nelson, *J. Biol. Chem.*, 1944, **153**, 375; Duff and Eastwood, *loc. cit.*). A synthetic glucose–fructose mixture containing 2·9% of glucose gave a recovery of 3·1% of glucose by this method.

Acetylation.—A specimen of polysaccharide (1·5 g.) was dissolved in dry pyridine (20 c.c.)

according to the method of Pacsu and Mullen (*J. Amer. Chem. Soc.*, 1941, **63**, 1487). Acetic anhydride (20 c.c.) was added with stirring during 7 hours and the solution left for 2 days. The acetylated fructosan was precipitated with water (1 l.) and washed with water, and the product dried in a vacuum-desiccator ($CaCl_2$), giving a white powder. After reprecipitation from chloroform with light petroleum (b. p. 60—80°), a fine white powder was obtained {1·8 g.; $[\alpha]_D^{16}$ +22° (*c*, 1·1 in $CHCl_3$); $\gamma_{sp.}^{20}/c' = 1{\cdot}09$ where *c'* is the concn. in moles of the unit $C_{12}H_{16}O_8$ per l.} (Found : Ac, 43·1%).

To a solution of this acetyl derivative (0·5 g.) in chloroform (2·5 c.c.), cooled in a freezing mixture, a solution of sodium (0·25 g.) in absolute methanol (1 c.c.) was added (cf. Zemplen and Pacsu, *Ber.*, 1929, **62**, 1613). The mixture was shaken for 5 hours and ice-water (1 c.c.) added, followed by acetic acid (0·5 c.c.; 10%). Water (4 c.c.) was then added and the solution left to separate overnight. The regenerated fructosan was precipitated from the aqueous layer, with methanol. The product (0·22 g.) showed $[\alpha]_D^{15}$ −40·2° (*c*, 1·1 in H_2O) and mild acid hydrolysis followed by chromatographic examination showed the presence of fructose and glucose only.

Periodate Oxidation.—The fructosan (0·2864 g.) was dissolved in water (35 c.c.) and sodium metaperiodate (15 c.c.; 0·3M) added. The periodate uptake, determined by the arsenite method, was constant after 1 day at a value of 1·02 moles of periodate per $C_6H_{10}O_5$ residue.

Oxidation with potassium metaperiodate gave the following results (expressed as the number of $C_6H_{10}O_5$ residues per mole of formic acid liberated) : 22·8 (73 hr.); 21·4 (100 hr.); 20·3 (126 hr.); 19·5 (171 hr., const.).

The phenylhydrazine hydrochloride–potassium ferricyanide colour reaction with the solution of periodate-oxidised polysaccharide was negative, indicating the absence of formaldehyde.

Methylation.—The fructosan (10 g.) was methylated in the usual way with methyl sulphate and sodium hydroxide solution under nitrogen at room temperature. After the first methylation, the partly methylated material was separated, dispersed in acetone, and further methylated with methyl sulphate and sodium hydroxide solution. The methylation in acetone was repeated twice, giving a product (9 g.) showing OMe 44·6%.

Fractionation of the methylated fructosan was effected by refluxing chloroform–light petroleum (b. p. 40—60°) mixtures of varying composition. The following results were obtained.

Fraction	% $CHCl_3$ in solvent	$[\alpha]_D^{15}$ (*c*, 1·1 in $CHCl_3$)	OMe, %	Wt. (g.)
1	27	−54°	45·3	0·4
2	30	−54	45·3	0·6
3	32·5	−56	45·2	4·5
4	35	−56	45·5	1·6

Fractions 1, 2, and 4, together with some unfractionated material, were combined and methylated with silver oxide and methyl iodide to give a product (Fr. X) which showed OMe, 45·4%, $[\alpha]_D^{16}$ −54·4° (*c*, 1·2 in chloroform).

Hydrolysis of Methylated Fructosan.—The methylated fructosan (Fr. 3 above, 3·209 g.) was heated with methanol (100 c.c.) and water (34 c.c.) containing oxalic acid (1·35 g.) at 80° for 24 hours, and a little insoluble material (0·187 g.) was filtered off. Water (300 c.c.) was then added gradually and the water–methanol mixture removed at 40° under diminished pressure. The solution was reduced to its original volume and heated at 80° for 5 hours, neutralised with calcium carbonate, and filtered, and the filtrate evaporated to small volume at 35° under diminished pressure. The mobile syrup was extracted several times with boiling chloroform, and the extracts were combined, dried (Na_2SO_4), and taken to small volume. Examination of the resultant pale yellow syrup on the paper chromatogram, with butanol–ethanol–water solvent and developing sprays of aniline oxalate and urea oxalate, showed the presence of four sugars, corresponding to tetramethyl fructofuranose, tetramethyl glucose, a trimethyl fructose, and a dimethyl fructose, the latter being in very low concentration (R_G : 1·00; 1·00; 0·84; 0·62).

The insoluble material from the above hydrolysis, on further hydrolysis, gave paper chromatograms identical with those described above.

Separation of Methylated Sugars.—The sugars arising from the hydrolysis of fraction 3 were separated on a cellulose column (70 × 3 cm.) with light petroleum (b. p. 100—120°)–butanol (7 : 3), saturated with water, as eluant (Hough, Jones, and Wadman, *loc. cit.*), to give Fractions A and B.

Fraction A contained tetramethyl fructofuranose and tetramethyl glucose only. The tetramethyl fructofuranose (110 mg.) was estimated colorimetrically (Arni and Percival, *loc. cit.*), and hypoiodite oxidation showed that tetramethyl glucose was present to the extent of 17 mg.

Fraction A (OMe, 49·4%; n_D^{20} 1·4500) showed $[\alpha]_D^{17}$ +39° (*c*, 0·99 in H_2O). *Ca.* 40 mg. of this

fraction were oxidised with nitric acid and converted into the crystalline tetramethyl D-fructofuronamide, according to the method of Avery, Haworth, and Hirst (*loc. cit.*). After three recrystallisations from ether–light petroleum needles were obtained, of m. p. 99—101° (not depressed on admixture with an authentic specimen) (Found: C, 48·7; H, 7·7; OMe, 46·8. Calc. for $C_{10}H_{19}O_6N$: C, 48·2; H, 7·6; OMe, 49·8%).

The remainder of the syrup from fraction A was extracted with light petroleum (b. p. 35°), and both the extract and syrupy residue were taken to dryness. A speck of authentic crystalline tetramethyl glucose was added to the syrups, which were kept in a vacuum-desiccator over phosphoric oxide and paraffin wax, in a refrigerator for 3 weeks. The " extract " remained a syrup, but the " residue " crystallised partially. The crystals, separated on porous tiles, had m. p. 82°, not depressed on admixture with an authentic specimen of tetramethyl glucose.

Fraction B (2·211 g.) crystallised completely when kept at 0°. Chromatographic examination showed the absence of aldose. The sugar showed m. p. 73—75° after two recrystallisations from carbon tetrachloride–light petroleum, not depressed on admixture with authentic 1 : 3 : 4-trimethyl D-fructofuranose. It had $[\alpha]_D^{16}$ (*c*, 1·4 in H_2O) −27·4° (4 min.), −47·3° (20 min.), −56·6° (60 min.); −58·8° (5 hr.), −60·6° (20 hr.), −61·1° (68 hr., const.) (Found: C, 48·9; H, 8·4; OMe, 40·6. Calc. for $C_9H_{18}O_6$: C, 48·6; H, 8·2; OMe, 41·9%). Examination by hypoiodite oxidation showed the absence of aldoses. Periodic acid oxidation (Reeves, *J. Amer. Chem. Soc.*, 1941, **63**, 1476) gave 0·8 mole of formaldehyde per mole of trimethyl sugar, estimated as the formaldehyde–dimedon compound (m. p. and mixed m. p. 186—187°).

A very small third fraction (*ca.* 7 mg.) was also obtained from the column, chromatographic examination of which showed the presence of only one sugar travelling at the same rate as 3 : 4-dimethyl fructose.

Hydrolysis of Methylated Fructosan X.—The methylated fructosan (2·512 g.), prepared as detailed above, was hydrolysed with methanolic oxalic acid as before; the solution was neutralised with calcium carbonate and filtered. The filtrate was concentrated, methanol added, and the water–methanol mixture distilled off with constant addition of methanol. The volume was taken to *ca.* 5 c.c., methanolic hydrogen chloride (50 c.c.; 0·3%) added, and the whole shaken, set aside at room temperature for 3 hours, neutralised, filtered, and freed from methanol as before. The aqueous solution (50 c.c.) was extracted, in the presence of a little barium carbonate, with purified light petroleum (b. p. 38—40°) in a liquid-extractor (Brown and Jones, *loc. cit.*) for periods of 10, 12, and 16 hours. The three extracts were evaporated practically to dryness and hydrolysed separately with sulphuric acid (15 c.c.; N/5) for 6 hours at 80°. The first contained only ketose, but the second and third contained also small quantities of tetramethyl aldose. The hydrolysed extracts were combined, to give fraction *a*. The aqueous solution in the extractor was filtered, taken to small volume, and hydrolysed with sulphuric acid (250 c.c.; N/5) for 6 hours at 80°, to give fraction *b*. Chromatographic examination of the products showed a high proportion of trimethyl fructose, with small amounts of tetramethyl fructose and tetramethyl glucose.

Separation of Fraction a.—The sugars in this fraction were separated into two fractions, a_1 and a_2, on a cellulose column (60 × 1·8 cm.) with light petroleum–butanol as before. Fraction a_1 contained tetramethyl fructofuranose (60 mg.) and tetramethyl glucose (13·4 mg.) estimated as described above. Fraction a_2 (0·228 g.) crystallised completely; hypoiodite oxidation indicated the presence of a small quantity of aldose, but aldoses could not be detected on a paper chromatogram, run in benzene–ethanol–water (167 : 45 : 15) (Andrews, Hough, and Jones, *J.*, 1952, 2746), it having been shown that 1 : 3 : 4-trimethyl fructose and 2 : 3 : 4-, 2 : 4 : 6-, and 2 : 3 : 6-trimethyl glucoses were separated under those conditions. No dimethyl sugars were obtained from fraction *a*.

Separation of Fraction b.—Separation of this fraction into its components was attempted by elution through a cellulose column (66 × 2·2 cm.) with benzene–ethanol–water, this solvent having been found capable of separating tetramethyl glucose from tetramethyl fructose on the paper chromatogram. Three main fractions, b_1, b_2, and b_3, were collected. Fraction b_1 contained tetramethyl glucose, tetramethyl fructose, and a little trimethyl fructose, separated on 4 sheets of 3 M.M. filter-paper by the above-mentioned solvent. The tetramethyl fructose, estimated colorimetrically, amounted to 30·6 mg., whilst alkaline hypoiodite showed the presence of 29·0 mg. of tetramethyl glucose. The trimethyl fructose amounted to 22 mg. Fraction b_2 (1·862 g.) was twice crystallised from carbon tetrachloride–light petroleum and the supernatant liquors from each crystallisation combined and examined on the paper chromatogram; a small quantity of trimethyl aldose was observed (*ca.* 1 mg. as determined by alkaline hypoiodite oxidation). Fraction b_3 was a mixture of trimethyl fructose and dimethyl fructose, with a trace of trimethyl glucose; these were separated on a cellulose column (56 × 1·6 cm.), elution with

light petroleum–butanol (7 : 3) saturated with water as eluant and then with light petroleum–butanol (1 : 1) yielding trimethyl fructose, 36·0 mg., and dimethyl fructose, 16·4 mg.

Identification of Tetramethyl Glucose.—The aldose material from fraction b_1 after two crystallisations from ether–light petroleum (b. p. 40—60°) had m. p. 85°, not depressed on admixture with an authentic specimen of 2 : 3 : 4 : 6-tetramethyl D-glucose, $[\alpha]_D^{15}$ $+95° \longrightarrow +84°$ (*c*, 0·5 in H_2O) (Found : OMe, 51·4%).

Examination of Dimethyl Fructose.—This had R_G 0·61 [butanol–ethanol–water (40 : 10 : 50)], OMe, 27·2%, and n_D^{20} 1·4784.

Molecular Weight by Barger's Method.—Barger's capillary technique (*loc. cit.*) was employed to determine the molecular weights of the acetylated and methylated derivatives of the fructosan. Droplets of solutions of known concentration were compared with solutions of sucrose octa-acetate (1—6 × 10^{-3}M). No satisfactory results could be obtained with 4%, 2%, and 1% solutions of the acetate, but a 1% solution of the methylated fructosan (fraction 3) gave reproducible values between 3440 and 5160, the equilibrium point being found to be between concentrations of sucrose octa-acetate of 2 × 10^{-3} and 3 × 10^{-3}M. An attempt to increase the accuracy of the method by employing a 2% solution of the methylated fructosan was unsuccessful.

Autohydrolysis of the Fructosan.—The fructosan (0·184 g.) in distilled water (25 c.c.) showed the changes at 100° : $[\alpha]_D^{15}$ −40·1° (initial value), −37·5° (4·5 hr.), −36·7° (9 hr.), −34·3° (14 hr.), −42·4° (19 hr.), −48·9° (22 hr.), −84·4° (29 hr.), −86·2° (35 hr.). After 22 hours a portion (15 c.c.) of the solution was chromatographically examined. It contained fructose, glucose, and three oligosaccharides, one of which travelled at the same rate as sucrose. Elution of this sugar from the paper, followed by hydrolysis, gave a solution containing two sugars, which travelled on the paper chromatogram at the same rate as glucose and fructose respectively.

After 30 hours, the pH of the solution was 3·4 (initial value 6·1) owing to the formation of three acids, observed chromatographically on running samples of the solution in butanol saturated with 1·5N-ammonia (Reich and Lederer, *Biochem. J.*, 1951, **50**, 60) and developing with methyl-red–methylene-blue (Conway and Byrne, *Biochem. J.*, 1933, **27**, 419).

Thanks are expressed to the Department of Scientific and Industrial Research for a maintenance grant (R. G. J. T.), and to Imperial Chemical Industries Limited, Central Agricultural Control, for the supplies of *Dactylis glomerata* used in these investigations.

KING'S BUILDINGS, UNIVERSITY OF EDINBURGH. [*Received, October 3rd*, 1952.]

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67. *The Synthesis of Sugars from Simpler Substances. Part V.* Enzymic Synthesis of Sedoheptulose.*

By L. HOUGH and J. K. N. JONES.

An enzyme preparation from peas catalyses the reaction of D-erythrose (and its 2 : 4-ethylidene derivative) with triose phosphate to give sedoheptulose, identified as sedoheptulosan and its tetrabenzoate. In the presence of the enzyme preparation dihydroxymaleic acid and triose phosphate yielded D-xylulose which was recognised as its crystalline *iso*propylidene derivative. A preliminary account of these results has appeared elsewhere (Hough and Jones, *Chem. and Ind.*, 1952, 907).

IN Parts III and IV * it has been shown that certain hydroxy-aldehydes combine with triose phosphate in the presence of an enzyme preparation from the pea (Stumpf, *J. Biol. Chem.*, 1948, **176**, 233), presumably by aldol condensation, to give monosaccharides containing the D-xylulose configuration on $C_{(1)}$, $C_{(2)}$, $C_{(3)}$, and $C_{(4)}$. On this evidence reaction of D-erythrose with triose phosphate would be expected to give sedoheptulose (D-*altro*-2-ketoheptitol). We have now isolated this sugar from the condensation of D-erythrose and of its 2 : 4-ethylidene derivative with triose phosphate. The heptulose was isolated by partition chromatography on cellulose and was characterised by its colour reactions (Nordal and Klevstrand, *Acta Chem. Scand.*, 1950, **4**, 1320), and as the crystalline 2 : 7-anhydro-derivative, sedoheptulosan, and its crystalline tetrabenzoate. This identification was

* Part IV, L. Hough and J. K. N. Jones, *J.*, 1952, 4053.

facilitated by a generous gift of sedoheptulosan, for which we thank Dr. N. K. Richtmeyer (cf. Pratt, Richtmeyer, and Hudson, *J. Amer. Chem. Soc.*, 1952, **74**, 2200). The heptose was isolated as the free sugar and not as the phosphate because the enzyme preparation contained phosphatase (cf. Hough and Jones, *J.*, 1952, 4050). Horecker and Smyrniotis (*J. Amer. Chem. Soc.*, 1952, **74**, 2123) observed the formation of heptulose phosphate from D-erythrose, hexose diphosphate, and aldolase from yeast and rat liver. The synthesis of this heptulose is of interest because it occurs in the free state in plants of *Primula* and *Sedum* species, in the plant family *Saxifragaceae* (Nodal and Oiseth, *Acta Chem. Scand.*, 1952, **6**, 446), in yeast (Robison, Macfarlane, and Tagelaar, *Nature*, 1938, **142**, 114), and because it appears to be one of the primary intermediates involved in carbon dioxide fixation (Benson, Bassham, and Calvin, *J. Amer. Chem. Soc.*, 1951, **73**, 2970; Benson, Kawauchi, Hayes, and Calvin, *ibid.*, 1952, **74**, 4477). As triose phosphate will also combine with propaldehyde and acetaldehyde (Meyerhof, Lohman, and Schuster, *Biochem. Z.*, 1936, **286**, 301, 319) in the presence of the pea enzyme preparation (Hough and Jones, unpublished results), it is very probable that other aldehydes such as, for example, tartronic aldehyde, $CHO{\cdot}CH(OH){\cdot}CO_2H$ would also undergo condensation under these conditions. The last compound would give rise to 5-keto-D-gluconic acid, an epimer and possible precursor of D-glucuronic and D-mannuronic acid (cf. Fischer, Baer, and Nidecker, *Helv. Chim. Acta*, 1937, **20**, 1226). While these observations throw some light on the possible mode of formation in plants of sugars with the D-xylulose configuration, the origin of D-galactose, L-arabinose, D-galacturonic acid, chondrosamine, and D-mannoheptulose, sugars which may be derived from ketose precursors with the L-ribulose configuration, is unknown.

A further problem is raised by the synthesis of sedoheptulose, namely, the origin of D-erythrose. Glycollic aldehyde is known to dimerise in the presence of lime water to give tetrose (Jackson, *J.*, 1900, 129). We considered it possible that D-erythrose might arise by the enzymic dimerisation of glycollic aldehyde. Accordingly, we re-examined the mixture of sugars produced by condensing glycollic aldehyde with triose phosphate in the presence of a crude pea enzyme extract, but we could find no trace of heptulose. It has been suggested that dihydroxymaleic acid is a possible precursor of glycollic aldehyde and tartronic aldehyde in the plant (cf. Hough and Jones, *Nature*, 1951, **167**, 180) and therefore it was of interest to study the reaction of dihydroxymaleic acid (sodium salt) and triose phosphate in the presence of the enzyme preparation. From this reaction D-xylulose was isolated and identified as its crystalline *iso*propylidene derivative, but no heptulose or uronic acid could be detected in the mixture. Apparently the dihydroxymaleic acid is decarboxylated enzymically to glycollic aldehyde (cf. Neuberg and Kerb, *Biochem. Z.*, 1913, **53**, 406) which then undergoes condensation to ketopentose. Whilst the possibility that D-erythrose arises from glycollic aldehyde cannot yet be ruled out, it is conceivable that the tetrose may arise from a ketohexose by fission between $C_{(2)}$ and $C_{(3)}$ just as a ketopentose derivative has been shown to split into glycollic aldehyde and glyceraldehyde derivatives (Rappaport, Barker, and Hassid, *Acta Biophys.*, 1951, **31**, 326). It might arise by reduction of dihydroxyacetoacetic acid as suggested by Benson, Kawauchi, Hayes, and Calvin (*loc. cit.*). It is of interest to note that these authors have observed that during photosynthesis fructose and sedoheptulose phosphates are synthesised concurrently, followed by ribulose phosphate, and they suggest that pentose is formed from heptulose. The reverse process, the formation of sedoheptulose phosphate as a product of pentose phosphate metabolism has been observed by Horecker and Smyrniotis (*J. Amer. Chem. Soc.*, 1952, **74**, 2123). The formation of pentose was envisaged as arising from heptulose by fission between $C_{(6)}$ and $C_{(5)}$ (cf. the degradation of pentoses, Rappaport, Barker, and Hassid, *loc. cit.*).

Experimental

The following solvents were used in chromatographic separations on Whatman No. 1 paper: (*a*) ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4); (*b*) *n*-butanol–pyridine–water (10 : 3 : 3) and (*c*) *n*-butanol–ethanol–water (40 : 11 : 19), all v/v. *p*-Anisidine hydrochloride solution was used as spray, to detect sugars, unless otherwise stated. Optical rotations were determined at 20° and in water. Microanalyses are by Mr. B. S. Noyes of Bristol. M. p.s are uncorrected. Evaporation of solutions was carried out under reduced pressure.

Synthesis of Sedoheptulose.—(2 : 4-Ethylidene D-erythrose and D-erythrose were prepared from D-glucose by the method of Rappaport and Hassid, *J. Amer. Chem. Soc.*, 1951, **73**, 5524.) (*a*) D-Erythrose (from 4 : 6-ethylidene D-glucose, 5·5 g.) in water (25 c.c.) was mixed with hexose diphosphate (sodium salt, 5 g.) in water (25 c.c.), and the pea enzyme (from peas, 50 g.; for preparation see Part III, *loc. cit.*) in water (125 c.c.) added. The pH of the solution was 7·2. After 72 hours at 30° the solution was heated to inactivate enzymes, then filtered, and the filtrate de-ionised with Amberlite resins IR-120 and IR-4B. Chromatographic examination of the concentrated solution disclosed erythrose, ribose, fructose, heptulose, glucose, and an unknown substance moving at a slower rate than any known hexose. The solution was concentrated to a syrup (1·31 g.) which was separated on a column of cellulose, with butanol half-saturated with water as mobile phase (Hough, Jones, and Wadman, *J.*, 1949, 2511). Portions of the effluent were heated on paper with the orcinol reagent (Nordal and Klevstrand, *loc. cit.*), which gives a pure blue colour with ketoheptoses and a green colour with ketohexoses, and the appropriate fractions selected and concentrated. The resulting syrup (101 mg.) was examined on paper chromatograms; it was observed to contain fructose, sedoheptulose, and a little glucose. In solvent (*c*), the heptulose moved slightly faster than glucose and a little more slowly than fructose. In order to destroy fructose and glucose and to convert the heptulose into heptulosan, the syrup was heated with N-sulphuric acid (10 c.c.) for 5 hours, excess of barium hydroxide added, and the solution heated for a further 2 hours. The solution was filtered before and after acidification with dilute sulphuric acid, de-ionised with Amberlite resin IR-4B, and concentrated to a syrup (42 mg.), which crystallised on nucleation with sedoheptulosan hydrate; it had m. p. 100—101°, not depressed on admixture with an authentic specimen, $[\alpha]_D$ −136° (*c*, 1·4). Its rate of movement in solvent (*c*) was 2·2 relative to galactose, in solvent (*a*), 1·12 relative to arabinose, and in phenol saturated with water, 1·14 relative to rhamnose. The positions of the sugars were detected with the ammoniacal silver nitrate reagent. It was indistinguishable from an authentic specimen on paper chromatograms or by *X*-ray crystallographic examination (Found : C, 40·2; H, 6·2. Calc. for $C_7H_{12}O_6,H_2O$: C, 40·0; H, 6·7%).

(*b*) 2 : 4-Ethylidene erythrose (from 5·5 g. of ethylidene glucose) was mixed with hexose diphosphate (sodium salt, 5 g.) in water (25 c.c.), and the enzyme solution (125 c.c.) from peas (50 g.) added. After 72 hours the solution was heated, filtered, cooled, and de-ionised with Amberlite resin IR-120. The acidic solution (pH 1—2) was heated at 100° for 3 hours to remove combined ethylidene groups, cooled, filtered, and de-ionised with Amberlite resin IR-4B. The neutral solution was evaporated to a syrup (2·1 g.) and examined on paper chromatograms. The presence of erythrose, ribose, sedoheptulosan, fructose, sedoheptulose, glucose, and a sugar moving more slowly than galactose was indicated. The syrup was fractionated on a column of cellulose, with butanol half-saturated with water as effluent, and the fractions giving positive tests for heptulosan and heptulose collected. The heptulosan moved at about the rate of xylose in solvent (*c*) and gave a blue colour with the orcinol spray. The combined fractions (60 mg.) were treated with hot N-sulphuric acid and then with barium hydroxide as described above. After filtration, the solution was de-ionised and concentrated to a syrup (31 mg.) which crystallised. It was recrystallised from methanol and then (24 mg.) had m. p. 100—101°, not depressed on admixture with an authentic specimen of sedoheptulosan hydrate, $[\alpha]_D$ −132° (*c*, 0·8). The tetrabenzoate had m. p. and mixed m. p. with an authentic specimen 165° (cf. Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1952, **74**, 2199).

(*c*) Glycollic aldehyde (8·0 g.) from dihydroxymaleic acid (20 g.) in water (100 c.c.) was mixed with hexose diphosphate (12·5 g.; sodium salt) in water (50 c.c.), and the pea enzyme (from 100 g. of peas) in water (300 c.c.) was kept at 25° for 72 hours (pH of solution 7·2). The sugars (4·0 g.) were isolated as described earlier (Hough and Jones, *J.*, 1952, 4047) and fractionated on a column of cellulose with *n*-butanol half-saturated with water as effluent. Neither sedoheptulose nor sedoheptulosan could be detected.

(*d*) Dihydroxymaleic acid (sodium salt, 5 g.) was suspended in water (100 c.c.), and hexose diphosphate (sodium salt, 5 g.) in water (100 c.c.) added, followed by enzyme solution (120 c.c.) from peas (50 g.). The solution (pH 8·0) was shaken continuously at 35° during 72 hours. At intervals samples were withdrawn and heated with 12% hydrochloric acid; furfuraldehyde-producing materials were rapidly formed. The solution was adjusted to pH 6 by acetic acid and filtered. The filtrate was heated, filtered, cooled, de-ionised with Amberlite resin IR-120, and concentrated. Chromatographic examination of the solution indicated the presence of xylulose, ribose, fructose, and hexose phosphates. Uronic acids were not detected by the naphtharesorcinol spray (Forsyth, *Nature*, 1948, **161**, 239). The solution was then heated at 100° for 3 hours to hydrolyse phosphate esters, cooled, filtered, de-ionised with Amberlite resin IR-4B, and

evaporated to a syrup (0·51 g.). This syrup was fractionated on a cellulose column with *n*-butanol half-saturated with water as developer. The fraction containing ketopentose (70 mg.) was collected, evaporated to a syrup, and examined chromatographically. It contained ketopentose and ribose. Accordingly, it was dissolved in acetone (25 c.c.) containing hydrogen chloride (1% w/v). After 3 hours, chromatographic examination (solvent *b*) showed that the ketopentose had been converted into an *iso*propylidene derivative which moved with the solvent front (R_F 0·84, solvent *a*). The solution was neutralised (Ag_2CO_3), filtered, and concentrated, and the syrup (66 mg.), n_D^{25} 1·4625, fractionally distilled in a micro-distillation apparatus. The distillate (48 mg.), b. p. 120°/0·1 mm., n_D^{26} 1·4625, crystallised on nucleation with an authentic specimen of 2 : 3-*iso*propylidene D-xylulose. When recrystallised from pentane it had m. p. 68—71°, not depressed on admixture with authentic specimens kindly supplied by Professor T. Reichstein and The Rockefeller Institute for Medical Research (Levene collection of chemicals) $[\alpha]_D$ +6° (*c*, 2·2) (Levene and Tipson, *J. Biol. Chem.*, 1936, **115**, 731; Prince and Reichstein, *Helv. Chim. Acta*, 1937, **20**, 107).

Heptulose was not detected in later fractions emerging from the cellulose column.

Control experiments, involving D-erythrose and the enzyme preparation in one case, and D-erythrose and hexose diphosphate in another, at pH 7·5, were treated as described above. In neither case was heptulose produced.

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THE UNIVERSITY, BRISTOL. [*Received, October 22nd,* 1952.]

NOTES.

68. *Molecular Association of Oxygen and Aromatic Substances.*

By D. F. EVANS.

FRESHLY distilled dimethylaniline quickly becomes yellow in air; a much deeper colour is produced when oxygen is bubbled through the liquid. Such coloration has previously been attributed to permanent oxidation. It has been found, however, that the colour completely disappears when the dissolved oxygen is removed by a stream of nitrogen or by evacuation. Further, various aromatic substances develop a new absorption band (usually in the ultra-violet region) when saturated with oxygen at atmospheric pressure, and this band disappears when the oxygen is removed.

The spectra were measured at room temperature on a Unicam S.P. 500 spectrophotometer. The blank cell contained the pure compound or a solution of it in a neutral solvent, and the other cell a similar sample through which a stream of oxygen had been passed for some time. The spectra were measured as quickly as possible to minimise errors caused by changes in the concentration of oxygen.

The results obtained are shown in the Figure (except three bands which are omitted to avoid overcrowding) and the positions of the maxima are given in the legend; because of the intense absorption of aromatic compounds, the latter are not very accurate, although their relative positions will not be appreciably in error. Thus, when the pure liquids were diluted with a

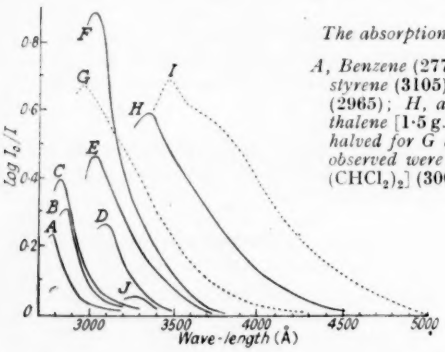
Anisole solutions (by vol.)				Benzene solutions	
	$\lambda_{max.}$ (Å)		$\lambda_{max.}$ (Å)		$\lambda_{max.}$ (Å)
30% in decalin	2950	10% in Bu^nOH	2915	20% in *cyclo*hexane	2735
10% ,, ...	2920	10% in $(CHCl_2)_2$	2935	20% in EtOH	2735

neutral solvent, the maxima shifted to shorter wave-lengths (see Table). It was shown, for the 10% solution of anisole in tetrachloroethane, that the effect was to a large extent

instrumental (possibly the result of stray radiation, see below) and due to the greatly increased transparency of the solution compared with that of pure anisole, by placing as filter a cell containing a 9 : 1 mixture (by vol.) of anisole and tetrachloroethane in front of both solution and blank cells. The maximum was then obtained at about 3000 Å, *i.e.*, almost the same as for pure anisole.

The intensities of absorption shown have no quantitative significance owing to large variations in the amount of dissolved oxygen, although such differences as between benzene and pyrrole are almost certainly significant.

Oxygen dissolved in carbon tetrachloride, and also ethyl benzoate and benzaldehyde (containing *meta*-directing and electron-accepting groups), gave no appreciable absorption down to 2550, 2700, and 3100 Å respectively. With " spectroscopic " hexane and *cyclo*hexane, absorption bands starting at about 2600 Å, with apparent maxima at about 2050 Å, were



The absorption spectra of oxygen dissolved in aromatic substances.

A, Benzene (2775); *B, chlorobenzene* (2865); *C, toluene* (2830); *D, styrene* (3105); *E,* m-*cresol* (3030); *F, anisole* (3005); *G, pyrrole* (2965); *H, aniline* (3350); *I, dimethylaniline* (3460); *J, naphthalene* [1·5 g. *in* 10 c.c. *of* $(CHCl_2)_2$] (3270). *Values of* $\log I_0/I$ *are halved for G and I. Figures in parentheses are* $\lambda_{max.}$ (Å). *Also observed were bromobenzene* (2885), *diphenyl* [1·5 g. *in* 10 c.c. *of* $(CHCl_2)_2$] (3005), *and quinol* (1·5 g. *in* 10 c.c. *of* Bu^nOH) (3260).

obtained (optical densities about 0·6 and 1·0). These maxima, however, are almost certainly not genuine, but due to the rapid increase in scattered light at shorter wave-lengths which results in low absorption values. Spurious maxima, which were shown to be due to this effect, have been observed in a similar spectral region and on a similar instrument, by Bladon, Henbest, and Wood (*J.*, 1952, 2737) and Eglington, Jones, and Whiting (*J.*, 1952, 2873). The true maxima with hexane and *cyclo*hexane will therefore lie at wave-lengths shorter than 2050 Å.

Since the positions of the peaks are almost unaffected by dilution of the aromatic component, it is unlikely that they are caused by an oxygen absorption band shifted by a solvent effect. More probably they are due to the formation of molecular complexes similar to those formed by aromatic substances and the halogens or sulphur dioxide (Benesi and Hildebrand, *J. Amer. Chem. Soc.*, 1949, **71**, 2703; Keefer and Andrews, *ibid.*, 1950, **72**, 4677, 7270; 1951, **73**, 462, 4169; Barb, *Proc. Roy. Soc.*, 1952, *A*, **212**, 66). These complexes give rise to absorption bands in a similar spectral region, which show a similar dependence on the nature of the aromatic substance. Thus for benzene derivatives their positions follow closely the electron-donating power of the substituent group or groups. This is particularly clearly shown in the case of oxygen, owing to the larger variety of compounds that can be studied. The nature of the halogen complexes has been discussed at length by Mulliken (*J. Amer. Chem. Soc.*, 1950, **72**, 600; 1952, **74**, 811).

It is of interest that oxygen complexes would provide a plausible initial stage in the oxidation, and especially the photo-oxidation, of aromatic substances such as phenols and amines. They may also be involved in certain cases of fluorescence quenching by oxygen.

The absorption obtained with hexane and *cyclo*hexane is unlikely to be due to the formation of complexes. It is more probable that it is due to absorption by the oxygen itself, possibly as a result of the forbidden $^3\Sigma_u^+ - ^3\Sigma_g^-$ transition being permitted to some extent by the intermolecular forces. In gaseous oxygen this transition gives rise to a series of extremely weak absorption bands starting at about 2700 Å, with a continuum at 2425 Å (Herzberg, *Canad. J. Phys.*, 1952, **30**, 185). The increase in intensity in going from gas to solution seems very large, however. A consequence of this absorption of some

practical importance is that hexane and *cyclo*hexane become considerably more transparent in the ultra-violet when deoxygenated.

Further work is in hand.

The author thanks Dr. R. E. Richards, under whose supervision this work was carried out, for help and advice, Dr. E. J. Bowen and Dr. L. E. Orgel for helpful discussions, and the Department of Scientific and Industrial Research for a Maintenance Grant.

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, August 9th*, 1952.]

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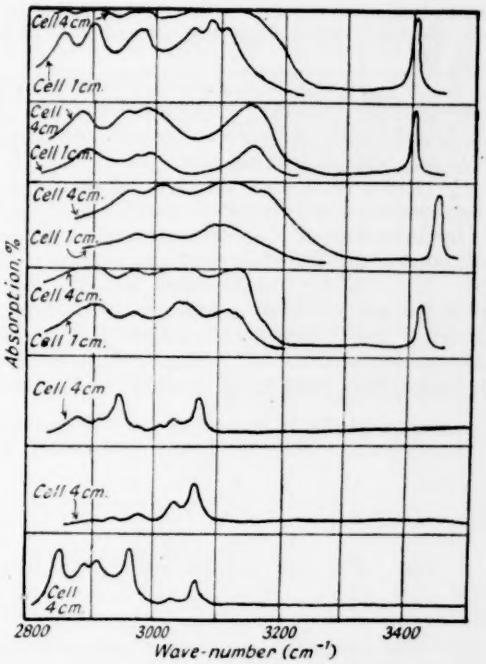
69. *The Infra-red Spectra of Some Thio-amides.*

By M. ST. C. FLETT.

DURING an investigation of the vibration frequency characteristic of the C=N group, we have measured the infra-red spectra of some compounds which are commonly formulated with the group ·N:C(SH)·. Randall, Fowler, Fuson, and Dangl (" Infra-red Determination



2-*Mercaptobenzothiazole*, 0·0072M.

2-*Mercaptothiazoline*, 0·0057M.

2-*Mercaptobenzoxazole*, 0·0043M.

2-*Mercapto*-4-*methylthiazole*, 0·0050M.

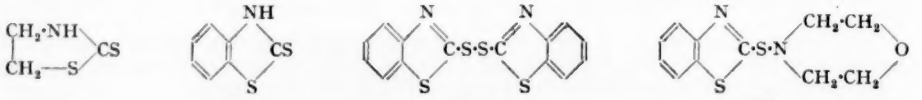
2-*Methylthiobenzothiazole*, 0·0055M.

Dibenzothiazolyl disulphide, 0·0030M.

2-*Benzothiazolylsulphenomorpholide*, 0·0042M.

of Organic Structures," Van Nostrand, 1949) have suggested from its infra-red spectrum that in the solid state 2-mercaptothiazoline has the structure (I). Also the infra-red spectrum of 2-mercaptobenzothiazole has been reported by Mann (*Trans. Inst. Rubber Ind.*, 1951, **27**, 232) who, from the absence of an S–H band, suggests the thio-amide structure (II), but finds no band which he can associate with an NH group. Our measurements on these and related compounds in the solid state and in dilute solution in carbon tetrachloride in the 3μ region, by use of a calcium fluoride prism, throw further light on this apparent anomaly. The figure shows the spectra in this region of solutions of 2-mercaptobenzothiazole, 2-methylthiobenzothiazole, 2-mercaptobenzoxazole, 2-mercapto-4-methyl-

thiazole, 2-mercaptothiazoline, dibenzothiazolyl disulphide (III), and 2-benzothiazolyl-sulphenomorpholide (IV).



(I) (II) (III) (IV)

There is a striking difference between the spectra of those compounds where there is a possibility of tautomerism involving ·NH·CS· and ·N:C(SH)· and those where the hydrogen atom is replaced. The former show a sharp band near 3430 cm.$^{-1}$ and very strong broad bands between 2900 and 3100 cm., whose strength makes it most unlikely that they are connected with either aromatic or aliphatic C–H links. Also, when the spectrum of 2-mercaptobenzothiazole was measured at various concentrations, the relative strengths of the sharp and broad bands varied with dilution. By analogy with the spectra of amides in solution (Richards and Thompson, *J.*, 1947, 1248), the sharp band is therefore assigned to the N–H vibration of monomers containing ·NH·CS· groups, and the broad band to modified N–H vibrations of hydrogen-bonded complexes in equilibrium with those monomers.

None of the spectra of the solids showed the sharp band near 3430 cm.$^{-1}$, but the strong absorption around 3000—3100 cm.$^{-1}$ persisted in those cases where a thio-amide structure was possible. In no case was a band near 2500 cm.$^{-1}$ found which could be associated with SH.

From these results it appears that each of the compounds 2-mercaptobenzothiazole, 2-mercaptobenzoxazole, 2-mercaptothiazoline, and 2-mercapto-4-methylthiazole exists in the solid state as hydrogen-bonded thio-amide complexes, which partially break down in carbon tetrachloride solution.

It is interesting that the N–H bands of the hydrogen-bonded form should be at the abnormally low wave-number of 3000—3100, and be so broad. This is in marked contrast to the behaviour of *N*-substituted amides (*idem, ibid.*) where values of 3430 cm.$^{-1}$ for the monomers and 3270 for the complexes were found. Clearly $>$N—H . . . O=C$<$ and $>$N—H . . . S=C$<$ bonds differ greatly, though it is hardly permissible to assume from the much greater frequency shift accompanying bonding in the latter case that N—H . . . S=C bonds are stronger. The spectral changes accompanying association of thio-amides resemble rather those of carboxylic acid dimerisation (Davies and Sutherland, *J. Chem. Phys.*, 1938, **6**, 755) than of amide association.

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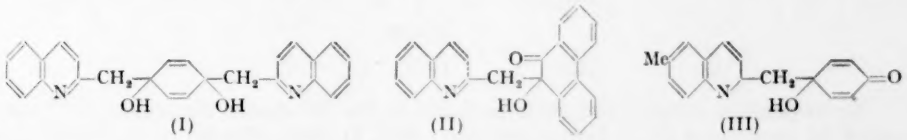
70. *The Interaction of Quinolines with Aldehydes and Ketones.*

By F. Bell.

The undermentioned compounds were prepared during an examination of the use of *m*-nitrobenzaldehyde for elimination of reactive quinolines from mixtures of coal-tar bases. When a quinaldine is heated with an equal amount of *m*-nitrobenzaldehyde at 120° for 6 hours the product is usually an alcohol; only on longer heating or on crystallisation from acetic anhydride does this pass into the styrene. This is contrary to the commonly held view (see, *e.g.*, Sidgwick's "Organic Chemistry of Nitrogen," Oxford Univ. Press, 1942, p. 554). Some experiments were made on the interaction of these bases with benzoquinone, phenanthraquinone and benzil.

Experimental.—2-*2′-Hydroxy-2′*-m-*nitrophenylethyl-lepidine*, after being washed with ethanol, crystallised from benzene in prisms, m. p. 165—167° (Found: C, 70·1; H, 5·1. $C_{18}H_{16}O_3N_2$

requires C, 70·1; H, 5·2%). On dissolution in boiling acetic anhydride it gave **2-*m*-nitrostyryl**-lepidine, m. p. 186°. **2-2′-*Hydroxy*-2′-m-*nitrophenylethyl*-6-*methylquinoline*** crystallised from benzene in almost colourless prisms, m. p. 142—144° (Found: C, 70·8; H, 5·5%), and similarly gave 6-methyl-2-*m*-nitrostyrylquinoline. **3-*Methyl*-2-m-*nitrostyrylquinoline*** crystallised from acetic anhydride in needles, m. p. 148—150° (Found: C, 74·6; H, 5·1. $C_{18}H_{14}O_2N_2$ requires C,



74·5; H, 4·8%), and the **7-*methyl*** isomer formed yellow needles, m. p. 192°, from benzene or acetic anhydride (Found: C, 74·0; H, 4·7%).

Quinaldine and benzoquinone at 150° (or in boiling xylene) reacted briskly to give a black product, readily purified by recrystallisation from xylene to yield almost colourless rosettes, m. p. 154°. This *compound* appears to be (I) (Found: C, 79·9; H, 6·1; N, 7·3. $C_{26}H_{22}O_2N_2$ requires C, 79·2; H, 5·6; N, 7·1%) for on dissolution in acetic anhydride and precipitation with water it gave quinol diacetate. Quinaldine and benzil gave **2-α-benzoylstyrylquinoline**, m. p. 191°, in poor yield (McElvain and Johnson, *J. Amer. Chem. Soc.*, 1941, **63**, 2213, give m. p. 187—188°).

Quinaldine and phenanthraquinone were heated at 200° (bath) for ¼ hour; cooling gave a black paste which was rubbed with ethanol, and the residue was filtered off and crystallised from benzene, yielding needles, m. p. 169°. Longer heating gave a tar from which it was not possible to isolate crystalline material. This compound (m. p. 165°) had been prepared previously by Benrath and Meyer (*J. pr. Chem.*, 1914, **89**, 266) by the long exposure of a mixture of quinaldine and phenanthraquinone to sunlight. They ascribed to it a rather improbable formula. Structure (II) appears more probable but, surprisingly, the compound crystallised unchanged from acetic anhydride. **2 : 6-Dimethylquinoline** with phenanthraquinone gave an analogous *compound*, m. p. 135° (Found: N, 3·8. $C_{25}H_{19}O_2N$ requires N, 3·8%), but α-picoline, **2 : 3-**lutidine, and **3 : 4-**lutidine did not react under these conditions.

2 : 3-Dimethylquinoline with benzil at 150° for 1½ hours gave **2-α-benzoylstyryl-3-methyl**-quinoline, m. p. 248°, previously described by Rohde (*Ber.*, 1934, **67**, 431).

2 : 6-Dimethylquinoline with benzoquinone gave a *compound*, which crystallised from xylene in rosettes, m. p. 137—139°, and for which structure (III) is suggested (Found: C, 76·5; H, 6·4; N, 5·4. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·7; N, 5·3%).

HERIOT-WATT COLLEGE, EDINBURGH. [*Received, August 28th*, 1952.]

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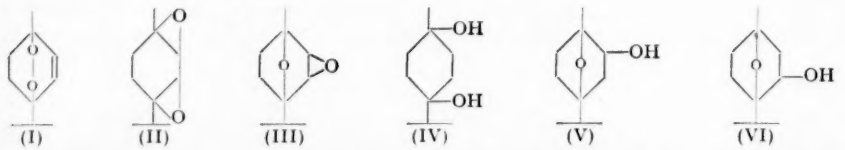
71. *Ascaridole Glycol Anhydride.*

By M. MATIC and DONALD A. SUTTON.

NELSON (*J. Amer. Chem. Soc.*, 1913, **35**, 84) suggested that ascaridole glycol anhydride obtained from ascaridole (I) at 150° was (II) and then probably passed into a more stable form (III) (cf. Thoms and Dobke, *Arch. Pharm.*, 1930, **268**, 128). The anhydride, prepared by isomerisation of ascaridole in boiling xylene (Henry and Paget, *J.*, 1921, **119**, 1714) and purified by vacuum-distillation, had no specific ultra-violet absorption bands and no hydroxyl groups, and appeared to be homogeneous. It was reduced by lithium aluminium hydride to a liquid mixture which was not resolved by vacuum-distillation but on counter-current solvent distribution separation yielded *ca.* 20% of ***cis*-1 : 4-terpin** (IV), independently of the time of heating during preparation of the anhydride. The oxiran rings in (II) thus seem established for at least part of the product. The other main reduction product had a higher partition coefficient but on evaporation of its aqueous solution yielded a trihydric alcohol, $C_{10}H_{20}O_3$, m. p. 162—163°, of lower partition coefficient. Formation of this is tentatively postulated as being due to hydration

of the internal 1 : 4-ether bridge of (V) or (VI) the expected products of lithium aluminium hydride reduction of (III).



(I) (II) (III) (IV) (V) (VI)

Hydrogenation of the anhydride in methanol at 150°/60 atm. in the presence of Raney nickel (cf. Newman *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 3362) afforded *ca.* 4% of *cis*-1 : 4-terpin together with at least two unidentified substances.

Experimental.—Ascaridole glycol anhydride. Ascaridole (77 g.) in xylene (50 c.c.) was added dropwise to boiling xylene (200 c.c.), and three such solutions were refluxed (at 650 mm.) for 6, 18, and 24 hours respectively. The isomerisation product (48 g.) (b. p. 76°/1 mm.) recovered by distillation through a column with an efficiency 15 theoretical plates (packed with Dixon rings; *J. Soc. Chem. Ind.*, 1949, **68**, 88) was easily separated from unchanged ascaridole in the forerun. The main fractions from the 6- and 18-hour preparations were split into a number of sub-fractions by distillation, but since these had almost identical refractive indices (n_D^{30} 1·4595—1·4602) they were recombined [Found: C, 71·4; H, 9·75; HO ($LiAlH_4$ method), 0. Calc. for $C_{10}H_{16}O_2$: C, 71·4; H, 9·5%].

Lithium aluminium hydride reduction. The anhydride (6-hour preparation) (3·11 g., 0·0185 mol.) and lithium aluminium hydride (0·55 g., 0·0145 mol.) in ether (2 hours' refluxing) gave a product (3·0 g.) (Found: C, 68·9; H, 11·5%) which on counter-current distribution [ethanol (20), water (30), *iso*hexane (30), and ethyl acetate (20). Craig, "Techniques of Organic Chemistry," Vol. III, 1950, Weissberger)] yielded *cis*-1 : 4-terpin, m. p. and mixed m. p. 117° (K = 0·32; 19%) (Found: C, 70·0; H, 12·0. Calc. for $C_{10}H_{20}O_2$: C, 70·0; H, 11·6%), and a solution of a substance of K 1·00 (19%). Evaporation of the latter gave a *triol*, m. p. 162—163° [Found: C, 64·1; H, 11·05; active H ($LiAlH_4$ in tetrahydrofuran), 1·45%; M (Rast), 185, 182. $C_{10}H_{20}O_3$ requires C, 63·8; H, 10·65; 3 active H, 1·6%; M, 188] (K 0·14).

The authors thank Mr. F. W. G. Schöning for carrying out the microanalyses. This note is published by permission of the South African Council for Scientific and Industrial Research.

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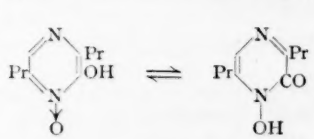
72. *Some* 10-*Substituted* 1 : 3-*Dimethyl*-2 : 9-*diazaphenanthrene* 9-*Oxides.*

By S. B. Hansen and V. Petrow.

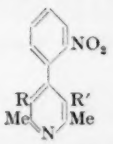
The hydroxamic acid group present in aspergillic acid (I) is responsible for its antibacterial action (Dutcher, *J. Biol. Chem.*, 1947, **171**, 321. Cf. 1-hydroxy-2-pyridone and -2-quinolone; Newbold and Spring, *J.*, 1948, 1864; Shaw, *J. Amer. Chem. Soc.*, 1949, **71**, 67; Lott and Shaw, *ibid.*, p. 70). We therefore prepared some tricyclic analogues.

Friedländer and Ostermaier (*Ber.*, 1881, **14**, 1916; Friedländer, *ibid.*, 1914, **47**, 3369) obtained 2-hydroxyquinoline 1-oxide as a minor product of reduction of ethyl *o*-nitrocinnamate with alcoholic ammonium sulphide. We find that zinc dust and ethanol readily convert diethyl 2 : 6-dimethyl-4-*o*-nitrophenylpyridine-3 : 5-dicarboxylate (II; R = R′ = CO_2Et) into 4-carbethoxy-10-hydroxy-1 : 3-dimethyl-2 : 9-diazaphenanthrene 9-oxide (III; R = CO_2Et, R′ = OH). Similar reductions of the appropriate pyridines gave 4-cyano-10-hydroxy-1 : 3-dimethyl- (III; R = CN, R′ = OH), 4-acetyl-1 : 3 : 10-trimethyl- (III; R = Ac, R′ = Me), 10-amino-1 : 3-dimethyl- (III; R = H, R′ = NH_2),

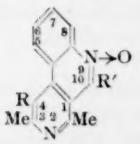
and 10-amino-4-cyano-1 : 3-dimethyl-2 : 9-diazaphenanthrene 9-oxide (III; R = CN; R′ = NH_2) (cf. Bauer, *Ber.*, 1938, **71**, 2226; Sharp and Spring, *J.*, 1951, 932). These oxides gave colours with ferric chloride, the first (but not the third) gave a blue copper salt,



(I)



(II)



(III)

and the last two gave reddish-brown precipitates with nickel salts. All liberated iodine from warm acidulated potassium iodide (cf. Newbold and Spring, *J.*, 1949, S 133). These reactions support their structures. In contrast to their monocyclic analogues (Spring and his co-workers, *loc. cit.*) they underwent profound decomposition on attempted acetylation.

Experimental.—M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.

4-*Carbethoxy*-10-*hydroxy*-1 : 3-*dimethyl*-2 : 9-*diazaphenanthrene* 9-*oxide* (III; R = CO_2Et, R′ = OH). Diethyl 2 : 6-dimethyl-4-*o*-nitrophenylpyridine-3 : 5-dicarboxylate (1·9 g.) (Hinkel, Ayling, and Morgan, *J.*, 1931, 1837) and ammonium chloride (750 mg.) in water (40 ml.) and alcohol (20 ml.) were treated at 60° with zinc dust (60 mg.), portionwise with stirring. After a further 1 hour concentrated hydrochloric acid (0·35 ml.) was added, stirring was maintained for 1 hour, and the crystalline solids were collected. Purification from methanol yielded 4-*carbethoxy*-10-*hydroxy*-1 : 3-*dimethyl*-2 : 9-*diazaphenanthrene* 9-*oxide* (75%), yellow needles, m. p. 180° (Found : C, 65·3; H, 5·0; N, 9·5. $C_{17}H_{16}O_4N_2$ requires C, 65·4; H, 5·1; N, 9·0%).

4-*Cyano*-10-*hydroxy*-1 : 3-*dimethyl*-2 : 9-*diazaphenanthrene* 9-*oxide* (III; R = CN, R′ = OH) was obtained (25%) from methanol in pale yellow needles, m. p. 230° (Found : C, 67·6; H, 4·0; N, 15·9. $C_{15}H_{11}O_2N_3$ requires C, 67·9; H, 4·1; N, 15·8%).

4-*Acetyl*-1 : 3 : 10-*trimethyl*-2 : 9-*diazaphenanthrene* 9-*oxide* (III; R = Ac; R′ = Me), after crystallisation from methanol, formed (35%) yellow plates, m. p. 218° (Found : C, 72·4; H, 5·6; N, 10·4. $C_{17}H_{16}O_2N_2$ requires C, 72·8; H, 5·7; N, 10·0%).

4-*Cyano*-1 : 3 : 10-*trimethyl*-2 : 9-*diazaphenanthrene* 9-*oxide*, pale yellow needles, m. p. 243—244° (from benzene) (Found : C, 72·8; H, 5·0; N, 16·4. $C_{16}H_{13}ON_3$ requires C, 73·0; H, 4·9; N, 16·0%), was obtained together with some 4-*cyano*-1 : 3 : 10-*trimethyl*-2 : 9-*diazaphenanthrene*, m. p. 217—218° (from alcohol) (Found : C, 77·3; H, 5·0; N, 17·3. $C_{16}H_{13}N_3$ requires C, 77·7; H, 5·3; N, 17·0%), by reduction of (II; R′ = Ac, R = CN) (Courts and Petrow, *J.*, 1952, 1) with stannous chloride in boiling hydrochloric–acetic acid.

10-*Amino*-1 : 3-*dimethyl*-2 : 9-*diazaphenanthrene* 9-*oxide* (III; R = H, R′ = NH_2) separated from ligroin–ethanol in yellow needles, m. p. 256—258° (decomp.) (Found : C, 69·8; H, 5·6; N, 18·1. $C_{14}H_{13}ON_3$ requires C, 70·3; H, 5·4; N, 17·6%).

10-*Amino*-4-*cyano*-1 : 3-*dimethyl*-2 : 9-*diazaphenanthrene* 9-*oxide* (III; R = CN, R′ = NH_2) was obtained (30%) from methanol in yellow spangles, m. p. 250° (decomp.) (Found : C, 67·7; H, 4·5; N, 19·8. $C_{15}H_{12}ON_4$ requires C, 68·2; H, 4·5; N, 21·2%).

The authors thank the Directors of The British Drug Houses Ltd. for permission to publish these results.

Research Laboratories, The British Drug Houses, Ltd.,
London, N.1. [*Received, September 11th*, 1952.]

73. *Influence of Temperature on the Spectrum of 9 : 10-Diphenylanthracene.*

By J. C. D. Brand and J. R. Davidson.

The colour of a solution of 9 : 10-diphenylanthracene is intensified by heat. This property was first attributed (Ingold and Marshall, *J.*, 1926, 3080; Schlenk and Bergmann, *Annalen*, 1928, **463**, 179; Schönberg, Ismail, and Asker, *J.*, 1946, 442) to the co-existence in equilibrium of a coloured biradical form of higher energy, but chemical evidence cited in support of this has been shown to be inadmissible (Barnett, Cook, and Wiltshire, *J.*, 1927, 1724) and it is now also known that the lowest triplet level of anthracene * is far too high to be thermally populated (Reid, *J. Chem. Physics*, 1952, **20**, 1214; Lewis and Kasha, *J. Amer. Chem. Soc.*, 1944, **66**, 2100); however, the spectroscopic explanation of the colour change has not been satisfactorily determined. From a qualitative spectral examination Dufraisse and Houpillart (*Bull. Soc. chim.*, 1938, **5**, 1628) suggested that the yellow colour arose owing to the proximity of the ultra-violet absorption system to the visible region; with rise in temperature, according to these authors, there is a general increase in intensity of absorption which causes the low-frequency tail of the ultra-violet band to spread into the visible region, leading to a temperature-dependent yellow colour. From the fact that no *new* absorption band appeared Dufraisse *et al.* concluded that the equilibrium postulated by Ingold and Marshall did not exist, but this inference was not entirely justified because, if it were correct that the intensity of the ultra-violet bands is temperature-dependent, there must be an equilibrium between two states of different energy to account for it.

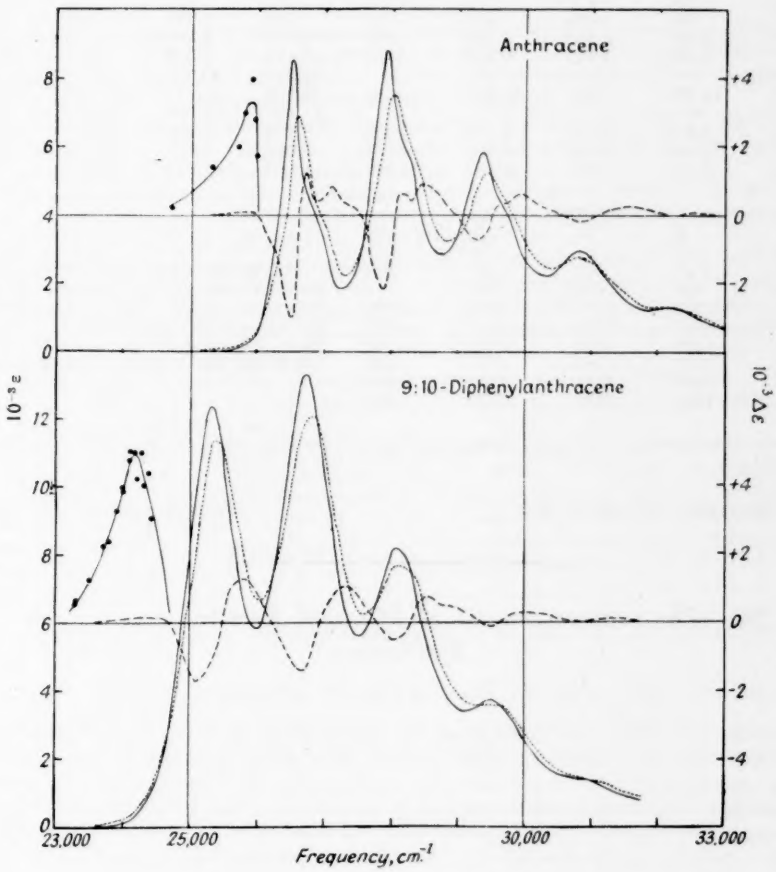
The spectra of anthracene and 9 : 10-diphenylanthracene, at 18° and 100°, are shown in the Figure. Contrary to the earlier suggestion, the integrated intensity of absorption ($\int \varepsilon d\bar{\nu}$) of 9 : 10-diphenylanthracene is *independent* of temperature, and this excludes the possibility that the yellow colour is associated with an equilibrium between two molecular states with different zero-point energies. Between 18° and 100° the only spectral change is due to the normal Franck–Condon broadening of the ultra-violet absorption, *i.e.*, to the change of transition probability resulting from the variation with temperature of the distribution of molecules over the vibrational levels of the ground state. With rising temperature, this effect leads to an increment of intensity where ε is small and a decrement where ε is large (Gibson, Rice, and Bayliss, *Phys. Review*, 1933, **44**, 193; Grubb and Kistiakowsky, *J. Amer. Chem. Soc.*, 1950, **72**, 419); these changes are recorded in the $\Delta\varepsilon$ curve in the Figure where it can be seen that the maxima in the vibrational envelope, including partially resolved maxima, correspond to minima in $\Delta\varepsilon$. With 9 : 10-diphenylanthracene the broadening on the low-frequency side of the first maximum (3950 Å) causes an increase of absorption in the visible region, the colour sensation at 100°, relative to 18°, being equivalent to that produced by a band having $\varepsilon_{max.} \sim 130$ at 4150 Å. The shape of the "difference" band in this region is shown on an enlarged scale in the Figure. The effect with anthracene is very similar but, with the loss of the phenyl substituents, the spectrum is displaced by about 1200 cm.$^{-1}$ to higher frequencies and the changes occur just outside the visible limit. One can understand, therefore, why thermochromism in anthracene derivatives occurs with bathochromic substituents other than phenyl (*e.g.*, with alkyl; Barnett, Cook, and Wiltshire, *loc. cit.*) and why groups such as *p*-methoxyphenyl and *p*-chlorophenyl, which are more powerfully bathochromic than phenyl, produce a greater depth of visible colour.

Experimental.—9 : 10-Diphenylanthracene, prepared by the method of Dufraisse and Le Bras (*Bull. Soc. chim.*, 1937, **4**, 1037), had m. p. 248·5° (uncorr.).

* 9 : 10-Diphenylanthracene should resemble anthracene closely in this respect, as in the singlet spectrum, because of the restriction on co-planarity (Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127).

Spectra. Extinction coefficients were measured with a Unicam SP 500 Spectrophotometer, fitted with a small electronically controlled thermostatic cell-compartment regulated to $\pm 0{\cdot}3°$. Water or glycol was used as bath-liquid. The wave-length calibration of the monochromator was slightly affected by conduction of heat from the thermostat and the calibration was referred to the Hg arc spectrum at both temperatures; the maximum difference observed with the bath at 100° was about 10 Å. The measurements refer to solutions in decalin, and the extinction

Spectra of anthracene and 9 : 10-*diphenylanthracene in decalin* (*temp.* 18° *and* 100°).



——— ε, 18°; – – – – – ε, 100°; — — — Δε; —●—●— Δε × 40.

	$f = 4{\cdot}31 \times 10^{-9}\int \varepsilon d\bar{\nu}$		Limits of integration ($cm.^{-1}$)
	at 18°	at 100°	
Anthracene	0·099	0·098	25,000—33,500
9 : 10-Diphenylanthracene	0·173	0·175	23,000—31,500

coefficients at 100° are corrected for expansion of the solvent (data of Grubb and Kistiakowsky, *loc. cit.*). No permanent change in the spectrum due to heating was detected when the solution was re-examined at room temperature (Table).

A A

Variation of ε with temperature (low-frequency region).

λ, Å (uncorr.)	(cm. mole l.$^{-1}$)$^{-1}$ ε_{18}	ε_{100}	ε_{18}	$\Delta\varepsilon$ *	(cm. mole l.$^{-1}$)$^{-1}$ ε_{18}	ε_{100}	ε_{18}	$\Delta\varepsilon$ *
	9 : 10-*Diphenylanthracene.*							
	Expt. 1				Expt. 2			
4250	—	59	13	+34	16	59	13	+33
4200	44	142	52	+60	47	133	50	+63
4150	198	410	214	+122	201	411	198	+119
4100	881	1,265	911	+110	873	1,275	885	+110
4050	3,237	3,480	3,252	−280	3,175	3,409	3,195	−240
4000	8,130	7,760	8,180	−1060	8,110	7,570	7,760	−1450
3970	—	—	—	—	11,380	10,080	11,400	−1600
3950	12,370	11,260	12,450	−1400	12,390	11,320	12,390	−1120
3930	—	—	—	—	11,700	11,120	11,550	−360
3900	8,210	8,840	8,110	+740	8,200	8,860	8,150	+1100
3850	5,880	6,730	5,860	+920	5,850	6,670	5,850	+940
3800	8,470	8,650	8,540	−500	8,480	8,470	8,480	−380
	Anthracene.							
4000	8	34	8	+23				
3950	16	51	16	+32				
3900	47	104	43	+53				
3850	428	600	460	0				
3800	4020	3269	4230	−1700				
3770	8410	6948	8380	−2600				
3750	5308	5802	5160	+1000				
3730	4081	4280	4090	+460				
3700	2840	3234	2762	+580				
3680	1855	2332	1855	+650				

* The figures in this column are corrected for change of wave-length calibration with temperature. Values of ε_{100}, however, are uncorrected and in general, therefore, $\Delta\varepsilon$ is not equal to the difference between col. 3 and the average of cols. 2 and 4.

Grants in support of this work from the Chemical Society and from D.S.I.R. are gratefully acknowledged.

THE UNIVERSITY, GLASGOW, W.2. [*Received, September 20th*, 1952.]

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74. *The Chlorostannates of Dimethyl Ketazine and Certain Hydrazones.*

By W. PUGH and A. M. STEPHEN.

WE recently (*J.*, 1952, 4138) described the preparation of compounds containing the hydrazinium and chlorostannate ions together with some aliphatic ketones, in which, pending crystal structural examination, the ketones were represented merely as solvent of crystallisation. Anomalies which appeared in the analysis of similarly prepared compounds of antimony and bismuth, to be reported later, have led us to re-examine the composition of these substances, to discard the 2 : 4-dinitrophenylhydrazine method of ketone estimation (Iddles and Jackson, *Ind. Eng. Chem., Anal.*, 1934, **6**, 454; Houghton, *Amer. J. Pharm.*, 1934, **106**, 62; Perkins and Edwards, *ibid.*, 1935, **107**, 208), and to apply the hypoiodite method (Messinger, *Ber.*, 1888, **21**, 3366; Goodwin, *J. Amer. Chem. Soc.*, 1920, **42**, 39; Cassar, *Ind. Eng. Chem.*, 1927, **19**, 1061) to the compounds with acetone and ethyl methyl ketone. Much higher values have thereby been obtained, necessitating the formulation of these compounds as chlorostannates of dimethyl ketazine and butanone hydrazone respectively. Combustion analysis confirms the new formulation. These substances are completely hydrolysed in acid solution, yielding hydrazinium ions and free ketone in the ion-mol. ratio 1 : 2 for the ketazine compound and 1 : 1 for butanone hydrazone. Correspondingly, the compounds with diethyl ketone and di-*n*-propyl ketone are to be formulated as chlorostannates of pentan-3-one hydrazone and heptan-4-one hydrazone.

Dimethyl ketazine has been shown to be completely decomposed in acid solution to a mixture of hydrazine salt (1 mol.) and acetone (2 mols.). Its basic character, difficult to demonstrate for this reason and because of its acid-lability (Frey and Hoffmann, *Monatsh.*, 1901, **22**, 760), and certainly unexpected in view of Gilbert's observation (*J. Amer. Chem. Soc.*, 1929, **51**, 3402) that it has no basic function in aqueous acetone, is now established by the preparation of its chlorostannate from aqueous acetone. In the presence of a small excess of hydrochloric acid, on the other hand, dimethyl ketazine and stannic chloride in acetone solution deposit slowly the isomeric chlorostannate of 3 : 5 : 5-trimethylpyrazoline, with 2 mols. of acetone as determined by Messinger's method (*loc. cit.*).

Experimental.—Samples of the compounds previously reported were either recrystallised or made afresh. Nitrogen was estimated as hydrazine (by the Dumas method in the pyrazolinium salt), and acetone and ethyl methyl ketone were determined by Messinger's method after distillation of the ketone from dilute acid solution.

Bis(dimethyl ketazinium) chlorostannate forms clear rhombs, m. p. 137—138° [Found : C, 26·1; H, 4·5; N, 10·0; Sn, 21·1; Cl′, 38·0; C_3H_6O, 42·2. $(C_6H_{13}N_2)_2SnCl_6$ requires C, 25·8; H, 4·66; N, 10·0; Sn, 21·3; Cl′, 38·2; C_3H_6O, 41·4%].

Bis(butanone hydrazonium) chlorostannate separates as tetragonal prisms, m. p. 90° [Found : C, 19·1; H, 4·4; N, 11·1; Sn, 23·3; Cl′, 42·1; C_4H_8O, 28·0. $(C_4H_{11}N_2)_2SnCl_6$ requires C, 19·0; H, 4·35; N, 11·1; Sn, 23·5; Cl′, 42·1; C_4H_8O, 28·5%].

Bis(pentan-3-one hydrazonium) chlorostannate forms rectangular prisms, m. p. 157° [Found : C, 21·4; H, 4·7; N, 10·6; Sn, 22·5; Cl′, 39·8. $(C_5H_{13}N_2)_2SnCl_6$ requires C, 22·5; H, 4·9; N, 10·5; Sn, 22·3; Cl′, 39·9%]. This compound and that described immediately below are very sensitive to atmospheric moisture; they smell strongly of ketone, which probably accounts for the low values for carbon and hydrogen.

Bis(heptan-4-one hydrazonium) chlorostannate separates as clear rhombs, m. p. 87—89° [Found : C, 28·2; H, 5·7; N, 9·45; Sn, 20·3; Cl′, 36·5. $(C_7H_{17}N_2)_2SnCl_6$ requires C, 28·5; H, 5·8; N, 9·5; Sn, 20·1; Cl′, 36·1%].

Addition of stannic chloride (0·6 c.c.) to a solution of dimethylketazine (0·8 c.c.) in light petroleum (b. p. 80—100°; freshly distilled over Na) gave a white solid. Mixing this with concentrated hydrochloric acid (0·5 c.c.) in excess of acetone–ether and allowing the solvents to evaporate caused deposition of *bis*-3 : 5 : 5-*trimethylpyrazolinium chlorostannate* (with acetone of crystallisation), m. p. and mixed m. p. 218—219° [Found, in material dried at 80° *in vacuo* : Sn, 17·6; Cl′, 32·0; C_3H_6O, 18·0. $(C_6H_{13}N_2)_2SnCl_6,2C_3H_6O$ requires Sn, 17·7; Cl′, 31·6; C_3H_6O, 17·2%].

We are indebted to Mr. R. von Holdt and Mr. M. C. B. Hotz for carrying out some of the analyses.

UNIVERSITY OF CAPE TOWN. [*Received, October 13th*, 1952.]

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75. *Eudesmic Acid : Its Identity with 3 : 4 : 5-Trimethoxybenzoic Acid.*

By A. J. BIRCH and (MRS.) P. ELLIOTT.

EUDESMIC ACID, m. p. 168°, was identified as its amyl ester in the oil of *Eucalyptus aggregata* by Smith (*J. Proc. Roy. Soc. N.S.W.*, 1900, **34**, 72). He assigned to it the formula $C_{14}H_{18}O_2$ (mol. wt. 218) (cf. Baker and Smith, " A Research on the Eucalypts," Sydney, 1920, p. 404), apparently on the basis of analyses of the silver salt (Found : Ag, 33·9, 33·3. Calc. for $C_{14}H_{17}O_2Ag$: Ag, 33·2%) and the " dibromide," m. p. 102—103° (Found : Br, 41·75. Calc. for $C_{14}H_{18}O_2Br_2$: Br, 42·6%). Smith converted the acid by hot nitric acid into an acid, m. p. 113°, considered to be probably cumic acid. He thought that eudesmic acid was an alkylcinnamic acid. About 30 mg. of Smith's specimen were available in the University collection and have now been proved to be 3 : 4 : 5-trimethoxybenzoic acid.

Several occurrences of this acid in Nature have been recorded, *e.g.*, in *Prunus virginiana* (Power and Moore, *J.*, 1909, **95**, 253), and its relation to gallic acid is obvious.

Experimental.—The eudesmic acid, which was probably more than fifty years old, had m. p. 164°, raised to 168° by crystallisation from water (Found: C, 57·0; H, 6·0. Calc. for $C_{10}H_{12}O_5$: C, 56·6; H, 5·7%), and undepressed by an authentic specimen of 3 : 4 : 5-trimethoxybenzoic acid obtained by the methylation of gallic acid. The methyl ester was prepared in refluxing methanolic sulphuric acid (10%) (1 hour), and crystallised from aqueous methanol as needles, m. p. 79°. Smith's analyses agree with this formulation (Calc. for $C_{10}H_{11}O_5Ag$: Ag, 33·8. Calc. for $C_{10}H_{10}O_5Br_2$: Br, 43·3%). The ultra-violet absorption ($\lambda_{max.}$ 262 mμ, ε 9970, in EtOH) indicates a carboxyl group attached directly to a benzene ring. The oxidation product was perhaps impure 1 : 2 : 3-trimethoxy-4 : 5-dinitrobenzoic acid (m. p. 126°), known to be thus formed from the trimethoxybenzoic acid (Will, *Ber.*, 1888, **21**, 612).

UNIVERSITY OF SYDNEY, N.S.W.

[*Received, October 20th*, 1952.]

OBITUARY NOTICE.

JACK CECIL DRUMMOND.

1891—1952.

DURING the night of August 4th—5th, 1952, Sir Jack Drummond, his wife, and their ten-year-old daughter Elizabeth were savagely murdered while camping near Lurs in the Basses Alpes. At the time of writing this notice neither the identity of the assassin nor the motive for this monstrous crime is known. It is particularly poignant that he should have met his death in such a manner in a country which he loved so well and in which he was so highly respected both as a scientist and as a man.

Jack Cecil Drummond, only child of Major John Drummond of the Royal Artillery, was born on January 12th, 1891. Both of his parents died during his early childhood and he was brought up by an uncle, a Crimean War veteran. He received his school education at Roan School, Greenwich, and at King's College School in the Strand. As a boy he was not robust and was unable to take much part in school sports. From an early age, however, he was keenly interested in nature study and photography, and there is little doubt that his interest in the latter hobby marked the beginnings of his interest in chemistry. His uncle was an enthusiastic gardener, and it seems probable that it was from him that Drummond first acquired the great love for gardening which remained with him all his life.

In 1909 he entered East London College (now Queen Mary College) and graduated three years later with a First Class Honours degree in Chemistry of the University of London. With his family background it is not surprising that he was interested in military matters, and while at college he became an enthusiastic member of the Officers' Training Corps. It was not long, however, before ill-health compelled him to resign from the Corps, and for the same reason he was later prevented from serving in the armed forces during the 1914—18 war. His inability to serve in the war was a source of deep and lasting regret to him.

For a few months after graduating Drummond carried out research at East London College under Professor J. T. Hewitt, and then the opportunity to embark on a career in biochemistry was provided when he was appointed to a research assistantship in the Department of Physiology at King's College, London. He remained in this post for a short period only; but it was an important period in determining his subsequent career, since he came into contact with two men, Dr. Otto Rosenheim and the late Professor W. D. Halliburton, who exerted a profound and lasting influence upon him. There is no doubt that it was Rosenheim who first awakened Drummond's interest in the then-embryonic subject of biochemistry, and who taught him the value of the organic chemist's approach to biochemical and physiological problems—a lesson which he learned well and passed on in due course to his own pupils—while his subsequent interest in food chemistry and nutrition was to a considerable extent due to Halliburton's influence. His association with Rosenheim and Halliburton continued for many years after he had left King's College, and during the later years of his life he often spoke of both in terms of affection, gratitude, and respect.

The first task assigned to Drummond at King's College was that of assisting Dr. William Bain in an investigation of the pressor bases in normal urine, in the course of which *iso*-amylamine was successfully isolated. Bain's indebtedness to his young assistant was acknowledged in the following words: "I owe a great deal to his knowledge of chemical technique, without which my results would have been impossible" (*Quart. J. Exp. Physiol.*, 1914, **8**, 229). Also during his short stay at King's College Drummond collaborated with Rosenheim in devising the well-known volumetric benzidine method for the determination of sulphates in urine (*Biochem. J.*, 1914, **8**, 143), a method which Drummond later adapted to a micro-scale (*ibid.*, 1915, **9**, 492).

After leaving King's College Drummond worked for a few months as an Assistant Analyst in the Government Laboratory, and then in 1914 was appointed as assistant to Dr. Casimir Funk at the Research Institute of the Cancer Hospital in Fulham Road. His association with Funk, who at that time was attempting to isolate the "antineuritic vitamine" from rice polishings, was one of the several influences which were responsible for his subsequent interest in nutritional problems. At that time the importance in animal nutrition of the amino-acid make-up of dietary proteins and of certain so-called "accessory growth-promoting substances" had only recently been revealed, and in the circumstances, therefore, it was natural that Drummond should have decided to investigate the possible effects of amino-acid and accessory-food-factor

deficiencies on the growth rate of tumours in experimental animals. The results of this work (*ibid.*, 1917, **11**, 325) were negative in so far as he showed that tumours may continue to grow at the expense of the host, even though the growth of the latter is entirely inhibited by dietary restrictions. However, in the course of this and preceding work he had made himself master of the animal-feeding technique, and accordingly, when Halliburton, as a member of the Food (War) Committee of the Royal Society, required assistance in *ad hoc* investigations of the nutritional value of various fats, he invited Drummond to collaborate with him. These investigations (*J. Physiol.*, 1917, **51**, 235; 1919, **52**, 95, 328) marked the beginning of Drummond's long-maintained interest in the " fat-soluble A " accessory food factor. Subsequently, while still at the Cancer Hospital, he independently carried out preliminary investigations on the nature of the " fat-soluble A " factor (*Biochem. J.*, 1919, **13**, 81), and was one of the first workers to show that a deficiency of this factor results in a marked lowering of the resistance of experimental animals to bacterial infections (*ibid.*, p. 95). During the same period he also carried out a very painstaking and laborious investigation of the amino-acids in tumours (*ibid.*, 1916, **10**, 473), and made some preliminary studies on what was then known as the " water-soluble B " accessory food factor (*ibid.*, 1917, **11**, 255; 1918, **12**, 25).

In 1918 he was awarded the degree of Doctor of Science by the University of London for a thesis on " A Comparative Study of Tumour and Normal Tissue Growth," and in the same year he was appointed to succeed Funk as Director of Biochemical Research at the Cancer Hospital. By this time his reputation as one of the most talented and energetic young biochemists in the country was securely established, and in the following year, when R. H. A. Plimmer resigned his Readership in Physiological Chemistry at University College on being appointed to the Chair of Chemistry at St. Thomas's Hospital, Drummond was the obvious choice to succeed him. Three years later, at the early age of thirty-one, he was appointed to the newly-created Chair of Biochemistry at University College.

The Department which Drummond created at University College, although small and never in his own time an independent autonomous one, soon became recognized as one of the most important centres of biochemical teaching and research in the country and exerted an influence on the development of biochemistry out of all proportion to its size. At first much of the work was concerned with nutrition, but Drummond's policy was to encourage his more senior colleagues and pupils to develop independent lines of research of their own, and thus the interests of the Department rapidly broadened. Drummond believed that it was an important part of his duties as a professor to train men for senior posts elsewhere, and so successful was he in doing this that no fewer than nine of those who were his colleagues or pupils now hold or have held chairs. The secret of Drummond's success as a professor lay not only in his personal qualities as a teacher and research worker, but also in his happy knack of being able to inspire those who worked with him with something of his own attitude towards teaching and research. He himself was a brilliant lecturer, and it is no coincidence that many of those who were his pupils at University College later established reputations for themselves as good teachers.

Throughout his University College days Drummond's own research interests were largely, but by no means exclusively, centred around vitamin A. His work in this field was carried out not only in collaboration with assistants in his own Department, but also with workers from elsewhere including his old friend Rosenheim, S. S. Zilva of the Lister Institute, J. Golding of the Research Institute for Dairying at Reading, and I. M. Heilbron, R. A. Morton, and T. P. Hilditch of Liverpool University. Drummond always appreciated the practical importance of the distribution of the vitamin in animal and vegetable fats, and over the years he published a large number of papers on this topic. His joint monograph with Professor Hilditch on " The Relative Values of Cod-liver Oils from Various Sources " (H.M.S.O., 1930) published on behalf of the Empire Marketing Board contains a wealth of data, the value of which to the cod-liver oil industry can hardly be overestimated.

Drummond and Rosenheim were among the earliest workers to suggest that vitamin A might be related to the carotenoid pigments (*Lancet*, 1920, I, 862), but in his own subsequent work in this field he was the victim of circumstances and misfortune. His early feeding experiments with carotene were carried out at a time before vitamins A and D had been clearly differentiated and before it was known that both factors are necessary for normal growth in young rats; and in his later experiments (*J. Soc. Chem. Ind.*, 1929, **48**, 316T; 1930, **49**, 291T) he was unfortunate enough to select ethyl oleate as a vehicle for the administration of the carotene, a solvent in which the latter is rapidly autoxidized.

The part played by Drummond in the development of the invaluable antimony chloride colour reaction for vitamin A never received the recognition which it deserved. As early as

1920 he and Rosenheim suggested that the chromogen responsible for the well-known transient purple colour given by cod-liver oil on treatment with sulphuric acid might be related to the vitamin (*Lancet*, 1920, I, 862), and later work with A. F. Watson indicated that this suggestion was well founded (*Analyst*, 1922, **47**, 341). In 1925 he and Rosenheim described the more sensitive and less transient colour reaction given by liver-oils with arsenic trichloride and provided strong evidence indicating a relation between the chromogen and the vitamin (*Biochem. J.*, 1925, **19**, 753). The following year the procedure was improved by Carr and Price (*ibid.*, 1926, **20**, 497) who substituted antimony trichloride for arsenic trichloride. In the circumstances it seems less than just that this colour reaction should have become generally known as the " Carr–Price " reaction rather than as the " Rosenheim–Drummond " reaction, particularly since Drummond himself in collaboration with R. A. Morton provided the first satisfactory evidence that the colorimetric method is a reliable means of determining the vitamin A potency of cod-liver oils (*ibid.*, 1929, **23**, 785).

Over the years Drummond and his colleagues made repeated attempts to isolate pure vitamin A from fish-liver oils and, although the distinction of being the first to achieve this was denied to him, it is probable that had it not been for his earlier work the final isolation of the pure vitamin would have been delayed for many years; and in this connection the value of his work on the colour reactions can hardly be overestimated. After two unsuccessful attempts to isolate the vitamin from fish-liver oils (*ibid.*, 1925, **19**, 1047; 1929, **23**, 274), Drummond made a third attempt in collaboration with Heilbron and Morton of Liverpool and a highly concentrated oily product was obtained which was approximately ten times more potent as a source of the vitamin than the purest carotene then available (*ibid.*, 1932, **26**, 1178). However, while this work was still in progress the isolation by Karrer and his co-workers (*Helv. Chim. Acta*, 1931, **14**, 1036, 1431) of a similar product, which they regarded as being approximately homogeneous, was announced. Although subsequent work was to indicate that neither product was absolutely pure, that fact in no way detracts from the magnitude and importance of the achievements of both groups of workers.

Next in importance to his work in the vitamin A field is, perhaps, Drummond's work on vitamin E. After preliminary work (*Biochem. J.*, 1935, **29**, 456) the preparation of an oily product from wheat-germ oil was reported, which, although not demonstrably homogeneous, appeared to be considerably more active than any that had hitherto been obtained (*ibid.*, p. 2510). The following year, after the isolation of α-tocopherol from wheat-germ oil as a crystalline allophanate by H. M. Evans and his co-workers (*J. Biol. Chem.*, 1936, **113**, 319) it was apparent that Drummond's product, unknown to him at the time, must have been the vitamin in a state approximating to purity.

From the mid 1930's onwards Drummond's interests tended to turn more and more towards problems of human nutrition. On the one hand he turned his attention towards various practical present-day nutritional problems (cf. Bull. Health Organ., League of Nations, Vol. VI, Ext. No. 11; *Lancet*, 1934, I, 757; *J. Soc. Chem. Ind.*, 1937, **56**, 191T), and on the other he became interested in the history of the changing dietary habits of the British people over the centuries. This latter interest culminated in 1939 in the publication, with Anne Wilbraham, of " The Englishman's Food " (Cape, London, 1939)—a scholarly and absorbingly interesting history of English diet from medieval times until the present day which some rate as his finest achievement.

Soon after the outbreak of the 1939–45 war Drummond was seconded from University College to act as Scientific Adviser to the Ministry of Food. He was uniquely well-suited for this post, not only by reason of his wide knowledge of the scientific aspects of human nutrition, but also because of his considerable experience with food manufacturers and his own personal qualities—in particular his tireless energy and ability to " get along " with people. Those who knew him well realised that this opportunity of serving his country in a capacity for which he was so well fitted afforded him deep personal satisfaction.

The burden of responsibility carried by the Minister and by his Scientific Adviser was a heavy one, and decisions affecting the health of the whole nation, and perhaps even the course of the war, had to be taken by the one on the advice of the other. It cannot be doubted that these decisions were wise ones when it is remembered that in spite of the greatly restricted importation of foods from abroad there was little or no malnutrition during the war; indeed in the opinion of many of those competent to judge, the nation as a whole, particularly the children and expectant and nursing mothers, had a more balanced diet during the war than before it. Many of the measures introduced during the war by the Ministry of Food, and for which Drummond was partly responsible, were of lasting benefit to the country; and among these should be

mentioned the improvement in the nutritional value of white bread, the fortification of margarine with vitamins A and D, and the extension of the milk and meals service in schools. On learning of his death on August 5th, Lord Woolton paid tribute to Drummond's work at the Ministry of Food during the war in the following words: "I shall ever be grateful to him for the knowledgeable and enthusiastic co-operation that he gave me. The nation is in his debt" (*The Scotsman*, August 6th, 1952).

During 1944—45 Drummond was Adviser on Nutrition, Allied Post-War Requirements Bureau and S.H.A.E.F., and Adviser on Nutrition, Control Commissions for Germany and Austria (British Element) during 1945—46. His war-time duties took him to Malta and to North Africa to study dietary conditions, and shortly before the cease-fire in Western Europe he headed a special Red Cross relief team which was given protected passage through the enemy lines to make a survey of the conditions amongst the starving inhabitants of Western Holland.

In recognition of his war services Drummond was knighted in 1944, made a Commander of the Order of Orange Nassau in 1947 and in the same year was awarded the U.S. Medal of Freedom with Silver Palm. In 1948 he was given the degree of Docteur (*honoris causa*) by the University of Paris. These honours possibly gave more pleasure and satisfaction to his many friends and admirers than to Drummond himself, since he was essentially a modest man with no particular ambitions for such distinctions.

Drummond's decision to resign from his chair at University College after the war to take up the appointment of Director of Research of Boots Pure Drug Company at Nottingham came as no surprise to those who knew him well. For some years before the war he had been unable to carry out as much laboratory research as he would have liked owing to lack of adequate financial support (cf. *Biochem. J.*, 1937, **31**, 1852), and there is no doubt that he welcomed the opportunity to direct research on a large scale which this post provided.

Drummond was a member of many scientific societies, including the Chemical, Biochemical, and Physiological Societies and the Society of Chemical Industry. He served on the Committee of the Biochemical Society from 1922 to 1927 and from 1939 to 1942, and was secretary from 1919 to 1922; at the time of his death he was one of the six trustees of this Society. In 1919 he was elected to a Fellowship of the Institute of Chemistry; he served on the Council of that body from 1926 to 1929 and from 1940 to 1943, and acted as an examiner for the fellowship continuously from 1929 to 1935. He was elected to a Fellowship of the Royal Society in 1944, and in 1946 he was made an honorary member of the New York Academy of Science.

It is not easy to write of Drummond the man at this time when the memory of the tragedy of his death is still fresh. Impulsive by nature and often outspoken, he had absolute intellectual integrity and never compromised on matters of principle when he knew he was right. He was a man of catholic tastes and interests; a talented amateur painter and sketcher himself, he was interested in art, music, books, the drama, the open air, good food and wine, and above all in his fellow men. Those who had the privilege of working under him at University College will remember him always as a well-loved chief and friend to whom it was the natural thing to give complete loyalty.

I am greatly indebted to the old friends and colleagues of the late Sir Jack who provided me with information about his early life and scientific career.

G. F. MARRIAN.

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DL-Proline	14/- G
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2-Thiouracil	37/- H
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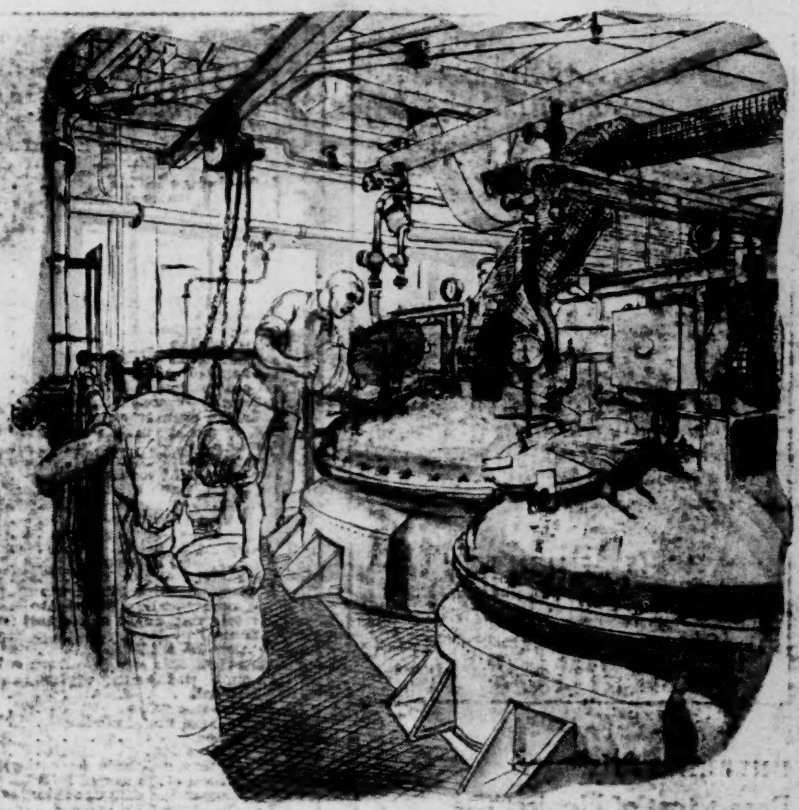

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